EREDITY

AND

DISEASE

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The Influence of Heredity on Disease, with special reference to Tuberculosis, Cancer and Diseases of the Nervous System

A Discussion

OPENED BY

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President of the Royal Society of Medicine
(INTRODUCTORY ADDRESS)

SIR WILLIAM R. GOWERS, M.D., F.R.S.
(DISEASES OF THE NERVOUS SYSTEM)

ARTHUR LATHAM, M.D.
(TUBERCULOSIS)

AND

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(CANCER)

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PREFACE

In view of the importance of determining the influence of Heredity as an etiological factor, the Council of the Royal Society of Medicine have thought it right to publish in a separate volume the discussion on this subject held at the Society's rooms on November 11, November 18, November 26, and December 2, 1908.

The Discussion was the first held by the Society in accordance with its intention to hold from time to time, in addition to the meetings of its individual Sections, meetings of the Society as a whole to discuss questions of general medical interest.

JOHN NACHBAR,
EDITOR.

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Royal Society of Medicine.

The Influence of Heredity on Disease, with special reference to Tuberculosis, Cancer and Diseases of the Nervous System.

An Address Introductory to a Discussion on the Subject.[1]

By Sir WILLIAM S. CHURCH, Bt., K.C.B.

President of the Society.

I MUST in the first place apologize to the Society and to the distinguished visitors who have favoured us with their presence to-day for having ventured to take upon myself the task of opening, or rather of introducing, this discussion. I can claim no special knowledge of the subject, and in truth I have only a very superficial and inadequate acquaintance with the various and varying theories that are and have been held on heredity. In fact, I am much in the same position, to make use of a common phrase, as the man in the street who, without any knowledge or acquaintance with the facts, supposes himself capable of forming an opinion on the most involved and difficult problems of diplomacy and politics; involved and difficult as they undoubtedly are, the complexity of the subject we approach to-day is much greater. There is, however, this difference in my position—that while he expresses his views with the utmost confidence, I only venture to do so tentatively and with the greatest diffidence.

The vast increase in our knowledge of the minuter forms of animal and vegetable life which has accrued during the last half century has thrown no light on the problem: What is life? Although there appears to me to be no inherent improbability in life arising *de novo* in our midst, yet no evidence has been brought forward, notwithstanding the laborious researches of Bastian, which satisfies the requirements of scientific investigators that such is the case. Harvey's dictum, if we

[1] The President opened the discussion on November 11, 1908, and it was continued on November 18, November 26, and December 2.

translate it into the language of Virchow, remains true and unchanged —*omnis cellula e cellulâ.*

The problem of heredity is scarcely, if at all, less obscure than that of life. The problem is well stated by Professor Poulton in his "Essays on Evolution": "How can a single germ-cell produce by repeated division an organism in which the somatic units of the parent are reproduced?"

The multiplication and reproduction of individuals is carried on by two distinct processes, viz., the sexual, as is the case (with a few remarkable exceptions) in all the higher organisms, and the asexual, which consists of the multiplication of individuals by spontaneous or artificial division. Passing by the multiplication of individuals by fission, the reproduction which takes place by budding, in some forms of life in which sexual reproduction is the rule, and the results of the experiments of Boveri and R. Hartwig appear to show that there is no essential difference between the phenomena of sexual and asexual reproduction. More remarkable still are the experiments of Loeb, who appears to have been successful in developing under certain conditions the unfertilized eggs of sea-urchins into normal larvæ, and those of Delage, who from non-nucleated fragments of the ova of certain echinoderms, molluscs, and annelids succeeded, by introducing into these fragments appropriate spermatozoa, in producing normal larvæ. From these experiments it appears that the presence of a nuclear body, whether it be that of a germ- or a sperm-cell, is sufficient to start, under certain conditions, growth and development in the ovum substance.

Darwin remarks: "The fertilized germ of one of the higher animals, subjected as it is to so vast a series of changes from the germinal cell to old age, incessantly agitated by what Quatrefages well calls 'tourbillon vital,' is perhaps the most wonderful object in Nature. It is probable that hardly a change of any kind affects either parent without some mark being left on the germ." It is the last part of this quotation which has been called in question, and on the answer given depends the conception formed of the problem of heredity.

Evolutionists, as far as I can understand them, are at the present time divided in two main schools: those who hold the view that acquired characters have no influence on the germinal matter, which they consider absolutely distinct from the somatic mass surrounding it, and those who hold that in some way or other the characters acquired by the somatic can influence the germinal matter.

The passage I have quoted may be taken as representing the view

taken of heredity by Darwin himself and his immediate followers; and he suggested his theory of pangenesis as a possible explanation of his views of heredity.

Professor Weismann is the illustrious head of the school which holds, if I understand Professor Weismann rightly, that the germ matter or plasm is continuous from one generation to another, and from it the germ-cells of each generation are successively derived, the germ-cells being endowed with a potentiality for variation within certain limits which can be called forth by an appropriate environment.

This opinion, that acquired characters are not transmitted, is no new one; it has been held by some ever since anthropology has been studied in a scientific manner, and no one has expressed it more clearly than my old teacher, Sir Wm. Lawrence, who says: "In all changes which are produced in the bodies of animals by external causes the effect terminates with the individual; the offspring is not in the slightest degree modified by them. Racial differences can be explained only by two principles: the occasional production of an offspring with different characters from those of their parents, as a native or congenital variety; and the propagation of such varieties by generation."

Professor Darwin, in his address to the British Association this year, set forth some of the difficulties which exist in accepting either the theory of pangenesis or that of the continuity of the germ-plasm as an explanation of heredity.

I confess that I am unable myself to see on what evidence the assumption of a specific difference between germ-plasm and somatic matter is made. It is clear, granting that germ-plasm is distinct from somatic matter, that it must be present in all parts of an organism that are in a state of growth, and it appears to me as reasonable an hypothesis to assume that germinal matter can be secreted or extracted from body matter as that it is continuous in its growth and periodically gives origin to germ-cells. The question before us is, With which theory do the facts best agree?

I have no intention, for I have not the necessary knowledge, to express an opinion on these different views, nor will I venture to enter on the subjects of Mutation or Mendelism, which have aroused so much interest and so much controversy in the scientific world during the last few years; but I should like to remark in passing that the various facts on which Mendel's laws are based were known to Darwin, although he did not work out the numerical proportions of the variations which he noted

Weismann himself has suggested that oscillation of nutrition in the soma-plasm may cause variations in the germ-plasm. If this is granted, it appears to me to admit the possibility, if not the probability, of heredity in disease. No disease which arises from or is associated with the presence of a foreign body, whether living or dead, within us can be considered hereditary, yet I believe it is a general view among breeders of stock that a tendency to various kinds of microbic disease exists in certain strains of blood which render them an easier prey to the specific micro-organisms causing disease than is the case with other strains of the same breed; in other words, they afford a more favourable home for the invading organism than do other families of the same stock. If this view be true, I think there must be many here who can give us information as to how far special microbic diseases appear to affect certain families among ourselves. There are, however, other forms of disease which, according to our present knowledge, arise from disordered metabolism within ourselves; and the question to-day is, how far the presence of these disorders can be ascribed to heredity, or are they acquired through forces acting on the individual affected? We have here to deal with a subject more difficult and complex than the form and structure of living organisms.

Chemical analysis of our tissues and their secretions yields us little or no information, and biochemistry is as yet in its infancy. The difference between the various enzymes or ferments present in our bodies cannot be shown by analysis of their component atoms, but how great are their differences of action! We do not at present know how far differences in their action may modify the rest of the body, but the connexion which appears to exist between disease of the thyroid gland and myxœdema, or between an abnormal condition of the pituitary body and acromegaly and giantism, are examples of how greatly the whole body may be influenced by abnormality in the functions of glandular organs. Dr. Garrod, in his interesting Croonian Lectures this year, delivered before the Royal College of Physicians, has drawn attention to the complex nature of what he terms "inborn errors of metabolism," and shows how increasing knowledge has modified the belief that oxidation was the sole agent in the metabolism of the component tissues of our bodies, and that the chemical changes which occur in them depend to a great extent on special enzymes, which act on the various constituents of our bodies. He also brings forward some evidence to show that certain errors in metabolism, such as cystinuria, alkaptonuria, and albinism, appear to run in families, and suggests that further research may determine how far their manifestation may be in accordance with Mendel's laws.

Immunity from diseases is connected with biochemical changes in our bodies, and as yet, so far as I know, no explanation has been given why toxins and poisons act differently in different species, as is seen, for example, in the action of morphia, atropine, and strychnine. Further, what grounds are there for thinking that a race can acquire immunity from attacks of microbic or other disease? Is the diminution of the frequency and mortality of phthisis which has been steadily taking place in this country for many years wholly due to improved sanitation and treatment, or is it commencing to die out owing to the acquirement of a measure of immunity by the race? To what was the diminution and extinction of leprosy in this country due? We can hardly ascribe it entirely to improved conditions of life. Moreover, different epidemics of disease, such as smallpox, measles, and scarlet fever, differ greatly in their severity. Is this due to the greater or less influence of the invading organisms or to a changed condition of the bodies invaded? These are questions which, unlike the problem of life, we may hope and expect that diligent research and careful labour may throw light on.

Cancer was very generally, and still is by many, considered as a typical example of an hereditary disease, but strong reasons have been adduced to show that this belief is not based on such sure grounds as was supposed. The most marked character which distinguishes cancerous from normal growth is the exuberance of cell-multiplication, and the nearest analogy to cancer in animals that we find in the vegetable kingdom appears to me to be in the growth of galls. I hope to hear from some cytologist how far the growth and development of the cells which form them have been studied, and how far the changes in their mode of growth resemble those met with in cancer in animals; and also how far the special form of irritation present may, in connexion with their site, determine the form and structure of the growths. Darwin was under the impression that the stimulus to growth was due in most cases to poison inserted with the ovum by the ovipositing insect; but later researches have shown that it is not the deposition of the ovum which is the determining cause of the hypertrophy which occurs, but that it is due to the embryo when hatched. The cells of the plant actually pierced by the ovipositing insect appear to die, and beyond the formation of a layer of cork round them little or no change takes place in the surrounding tissues until the embryo is hatched; then growing cells of the most varied description are formed with extraordinary rapidity, and assume a specific shape and character which is not always determined by the structure of the part affected; different, although closely allied,

species of gall-producing insects may cause galls with different and easily recognized peculiarities on the same leaf. Nevertheless the form and structure of the gall appear to depend rather on the constitution of the protoplasm affected than on the stimulus afforded by the presence of the insect. Is it unreasonable, when we see the wonderful action of these minute embryos—probably through some ferment secreted by them—on vegetable tissues, to suppose that some similar process may take place in cancer?—some innate error of metabolism, altering or forming some enzyme within us and causing a proliferation of cell-growth, its activity being called forth by some accidental irritation? The fact that mice in whom an inoculated tumour has been absorbed acquire immunity from further inoculation with tumour tissue appears to support this view, as does also the fact that the injection of normal mouse blood or of mouse embryo skin-emulsion also confers on mice a certain measure of immunity from cancer inoculation.

There is no class of disease in which the conviction that they are hereditary is more firmly fixed both among the lay public and the profession than many forms of diseases of the nervous system. To say that epilepsy, insanity, hysteria, and other neuroses are not inherited, but depend on the inheritance of a constitutional peculiarity, originating as a germinal variation which may manifest itself in different ways, appears to me to be a distinction without a difference. Further research and carefully recorded family histories are wanted before we can tell how far these various neuroses may be interchangeable or what may be the condition which determines the presence of any particular group of nervous symptoms. The epileptiform attacks in guinea-pigs whose nervous system has been traumatically injured have undoubtedly been transmitted to their descendants, and Professor Weismann, whilst admitting this, suggests various explanations which time will not permit me to enter on. There must, I think, be some present who can tell us if epilepsy or any other neurosis has been recorded as occurring with undue frequency in the offspring of those who have suffered from epilepsy induced by lead or other forms of poisoning.

Dr. Ormerod, in his recent Harveian Oration, has most ably pointed out how vast a field is open for the study of inherited peculiarities in diseases of the nervous system, therefore I will not take up your time by attempting to go over ground which he has so fully covered.

I am afraid that I have inadequately and very imperfectly placed before you the subject-matter for our discussion, and I now leave it to those who are better qualified than myself to carry it on. It is only by the accumulation of data, thoroughly sifted and openly discussed,

that we can hope to arrive at the probability of the correctness of any theory. I would urge on all who have the opportunity the desirability of recording family histories which appear to throw light on the subject, which is one of absorbing interest and has a direct bearing on the evolution and future welfare of mankind.

SIR WILLIAM R. GOWERS, F.R.S.[1]: May I venture, Sir, to express the feeling of obligation to you, which must be shared by all, for the lucid and pregnant words we have just heard, introducing the discussion we begin to-day. All must experience the sense of the transcendent mystery of life, to which you have eloquently referred, and the equal mystery of its transmission, carrying with it all its features, even often those of disease. Inscrutable its nature must ever be; its outward form alone can occupy us, and of that only a few of the more salient points have yet been seized.

The scientific study of heredity, which has undergone so remarkable a development since the mists were swept away which for long had hidden Mendel's work, cannot be applied fully to the diseases of man. The human race is not open to Mendel's essential methods, and its mere complexity of development involves innumerable differences from lower forms of life, the effects of which may be greater than we can well realize. Potential fallacies surround almost every inference that can be drawn. We can seldom look back far at preceding generations, and the future we must leave to those who may follow us. The difficulties of precision and fullness of knowledge are great, and the chance fertilization, from which the flowers of Mendel were guarded by his paper bags, is the rule in the human race, unalterable by us, however we may wish. Hence it seems useless even to apply the hereditarian terminology to facts that are in general inconsistent with its grounds. I can only hope to present a few of the general facts of heredity in some diseases of the nervous system, well known as they are, and I trust that they will be supplemented by others. We are only in the stage of random observation.

Among diseases of the nervous system are commonly included many that are not of it, but merely in it, and these can scarcely be discussed. Tumours of the brain and spinal cord are allied to morbid growths in general, for the most part. Yet many of them have a special relation to nervous tissue, such as gliomata, composed of the special interstitial elements of the nerve centres. Endotheliomata growing from the lining tissue of the cavities or on the surface of the brain and spinal cord, we do

[1] Sir William Gowers opened the discussion with regard to diseases of the nervous system.

not know how to class, whether with the centres in which they are found or with growths of the same character elsewhere. But all such affections are so rare that they have not yet justified any suggestion of heredity. This is also true of another condition in which heredity might reasonably be expected: the defect in the coarser formation of the spinal cord which leads to the cavities, and undeveloped adjacent embryonal tissue, of syringomyelia. It is sometimes found after death when there have been no symptoms to suggest it. When the causal arrest of development has occurred earlier and involved the enclosing structures, it constitutes a state often conspicuous in infancy—spina bifida. Heredity in these affections may be thought likely, but no ground for it has, I think, been discerned, and may not be until every member of the family can be scrutinized after death. Insular sclerosis is another affection in which heredity might be expected, according to one view of its nature, but no facts have suggested it.

Sudden cerebral seizures, apoplexy and the like, depend upon causes that take the heredity far away from the brain in which the lesion occurs; yet the frequency in which heredity is active is most notable. In some families many members suffer earlier in life than the malady is really common; but we must look to the vessels and the cause of their degeneration for the mechanism by which the disease is produced and through which heredity acts.

Toxic states, various in nature and origin, chemical and microbial, are potent causes of disease, but the range of their heredity in their occurrence is small. The so-called "inherited syphilis" has, of course, nothing to do with true heredity. I do not know of any observations on the children of those who suffer from it, and their life-histories. The question is important for our subject, and possibly some Fellows may be able to furnish us with facts. Any influence heredity may have on the liability to suffer from bacterial maladies affecting the nervous system may perhaps be suggested by the discussion on the similar facts regarding tubercle. The part it may play in the secondary production of chemical agents, from organisms acting on somatic processes, is an important problem; it is presented by the paralysis that sometimes follows diphtheria. The experience of our fever hospitals may furnish evidence for or against any family tendency to suffer from it. I think the tendency is not directly proportioned to the severity of the primary disease; there must be very many instances of several members of a family suffering from diphtheria, and it is most important that the records should be so kept as to facilitate observation of the disease in another generation of the same family. Such

search will be necessary in the case of many diseases, and nothing can be achieved unless suitable records are begun.

It would be wearisome even to enumerate the maladies from which we cannot expect to obtain knowledge, but I may mention one class of disease on which we may hope for some facts. Though they are not primarily of the nervous system, they often affect it gravely. There are those to which the President referred, that consist of deranged chemical processes in the vital laboratory of the human frame, giving rise to endogenous toxins. We see this in the nerve disturbance which occurs in diabetes, probably due to other material incidental to that by which the excess of sugar is produced, whether or not it is the same as that which often causes death. The heredity of diabetes is familiar, but its thorough study is a difficult task; a child not seldom suffers before a parent. The endogenous poisons of what we call gout are certainly many, and some also occur without the true constitutional state; both kinds may cause symmetrical symptoms in the extremities, but of their nature we know nothing. It cannot be doubted that the processes of the body are largely influenced by heredity.

The cases of disease of the nervous system in which the influence of heredity is marked seem to fall in certain classes. One of these consists of the early abiotrophies. I proposed this term some years ago as a convenient designation for the cases in which certain systems of structure, in the nervous or muscular system or elsewhere, have an essential defect of vital endurance, in consequence of which their life slowly fails. A marked example is presented by the hair follicles of the scalp, in consequence of which early and extensive baldness occurs in father and son (a convenient subject for the study of heredity). It is seen in the nervous system, as in hereditary optic atrophy, in which the onset is sometimes excited by some extraneous cause, inadequate alone to cause the enduring effect. Hereditary ataxy, or Friedreich's disease, is another instance, and so are the various myopathies. By "early" I mean those abiotrophies which begin before the development which coincides with growth is over, and often not many years after birth.

The muscles are not usually considered part of the nervous system, although they present a close relation to it in intimate structure. We may take the most typical form of pseudo-hypertrophic paralysis as a convenient instance of the heredity of the abiotrophies. The muscular fibres begin to waste during the first seven years of life, but the bulk of many of the muscles is actually increased by interstitial overgrowth of fibrous tissue and fat; certain muscles are small, and some may seem

absent from the first. This disease is due solely to heredity, but the heredity is maternal only; the affection never comes from the father. The tendency to it is thus germinal—a potential defect in part of the ovum, that part which will become the muscles of the male; but it is not usually in all the ova—some sons escape. The female children seldom suffer in this typical form, but they inherit the tendency, or some of them do, and their sons are prone to suffer. In the ova from which the daughters develop, the potentiality of the disease is not in the elements that develop into the muscles, but only in that portion of the protoplasm which will become their germinal tissue and form the muscles of male offspring. The same facts are true of other early atrophies, in hereditary optic nerve atrophy, &c.; sometimes they are limited to males, and are only transmitted by females. If the tendency is thus fixed in the germ-tissue, and differently fixed according to the resulting sex, does not the fact make it probable that the sex is also predetermined? Many have held this view, and it is not easy to see how otherwise the facts of these diseases can be explained.

The disposition of the disease seems seldom to be present in every ovum. Sometimes it apparently is in every male ovum. Every son has died, as in the well-known family described in the fifties by Dr. Meryon, but in that two daughters have failed to transmit the disease; another daughter has had two sons and three daughters—both the sons have died from it, all the daughters are free. In an instance which came under my notice long ago four sons died, but the fifth escaped, and his sons, of course, are free, but the only daughter, herself free, has her only two sons both affected.

We have many similar instances of the disease in two generations. We have known it just long enough—sixty years—to find it in a second generation, but it is curious how seldom we are able to trace the typical disease in preceding generations, although we are not often able to exclude it, from our lack of knowledge. I have met with it in the two sons of a lady (the third and sixth of seven sons), whose lineage and that of the mother of Meryon's cases can be obtained from the Peerage. This lineage presents a remarkable fact. Both were descended from a certain duchess who was married in 1774, and in the case of each the descent is solely in the female line. The mother of Meryon's cases I will call Lady A., and the other Lady B. Lady A. was the granddaughter of the said duchess, Lady B. is the great-great-granddaughter. There were sons in both lines, but from their ages at death in Lady B.'s family there can have been no case of the disease. In Lady A.'s

there is only one that suggests its possibility. A brother of hers died when aged 18, but some other cause is intrinsically more probable. We must, I think, regard it as of definite, though unknown, significance that both these maternal producers of the disease had a single ancestor, and considering the relation of the disease to sex, the descent by the female line cannot be regarded as an accident. I can offer no suggestion of its meaning. But it is remarkable how free from the disease the ancestors of those who produce it generally seem to be. We may note that isolated cases are more frequent than groups, although the groups comprehend a majority of the actual cases. When females suffer, males sometimes escape.

Only once have I known the disease to occur in the offspring of first cousins. There resulted four cases of albinism, one of whom had also pseudo-hypertrophic disease. Neither malady had occurred before. But there had been some previous instances of less close intermarriage during the preceding six generations, and considering the relation of the disease to the ovum, it can hardly be ascribed to the consanguinity of the actual parents. Of the origin of albinism I hope we shall hear more in the course of the discussion.

Other forms of myopathy have been traced through several generations. The facial form of Déjerine and Landouzy has been traced through five generations. This form often does not begin early, its progress may go on through life, and males may transmit it. The first series of Déjerine and Landouzy just mentioned bears a distant but interesting resemblance to Mendel's facts. A man and woman married, the woman being atrophic. They had one daughter, who was normal, who married a quite healthy man and bore three daughters, all affected. One of these married a healthy man and had two children, a girl (healthy), and a son, in whom the atrophy only showed itself when aged 26, and did not become general until the age of 50. He married a healthy woman and had nine children, six sons and three daughters. A son and a daughter died in childhood: of the remaining seven, four were atrophic, two sons and two daughters. If we regard the normal state as dominant and the atrophy as recessive, the absence of the latter in the second generation, recurrence in the third, and equality in the fourth and fifth, are noteworthy features.

I have dwelt on these muscular maladies because they present features that are well defined, and because most, if not all, the early nerve abiotrophies agree with them in origin, many even in the maternal heredity.

A second class may include the hereditary maladies which begin later in life, after the period of growth is over. They present persistent disturbance of function, and are commonly hereditary, but from either side. In the so-called heredo-ataxy of Marie the symptoms begin about the age of 30, and are usually fatal in about twenty years. It has been found to depend on atrophy of the cerebellum, associated with that of certain tracts of the spinal cord, at least in one case in which three generations were affected. Huntingdon's chorea begins usually in the senile period of life, but its heredity is well marked, and so is that of the peculiar rigidity called Thomsen's disease, a life-long peculiarity of action of the motor nerve structures, also called myotonia congenita.

I must pass some interesting diseases—paralysis agitans, tremors, Graves's disease, &c.—in which heredity can be traced seldom, but sometimes remarkably. I think it is probable that we shall hereafter find that special forms of heredity are associated with other characters in a manner that will make it an aid in distinguishing maladies that are now classed together; but for this we must wait.

A third class of diseases in which heredity is operative consists of the so-called functional affections. Some of them vary extremely in degree, and baffle attempts to group them so as to discover their relation to heredity. Such are hysteria and the defective nerve strength, which may manifest itself in varied ways, and which we are all drawn, sometimes against our better judgment, to designate "neurasthenia." Other functional disorders, such as chorea and neuralgia, have relations too complex for the clear discernment of heredity, and migraine, defined as it is, is connected with quite different constitutional states than disease of the nervous system. Two forms of functional disease have been much studied in relation to heredity: epilepsy and insanity; I propose to confine myself to epilepsy, leaving the relations of insanity to those who take part in the subsequent discussion.

Some cases of epilepsy are outside our subject. Those that result solely from organic lesions of the brain, from disease, or trauma, or difficult birth, are not concerned with heredity. I confess I have always acted on the belief that the tendency to convulsion in such acquired cases, without other evidence of disposition, may be regarded as not transmissible. I have never hesitated, on this ground, to permit the marriage of a sufferer, and I have not had any evidence to show that I was wrong in doing so, however early in life the damage arose. I do not question the guinea-pigs of Brown-Séquard; I do question an inference from guinea-pigs to men. But such cases of "organic

epilepsy" are rare. They constitute so small a proportion of the cases as to have little influence on statistics of heredity. The difficulties in ascertaining the facts of family histories are vast. Among hospital patients genuine ignorance often hinders. A woman brought her son for epilepsy, and denied that any of his relations had had fits. As soon as she had gone out of the room she returned with two of his brothers suffering from them. It had not occurred to her that a brother is a relation. In patients seen in private the stigma supposed to attach to some diseases leads to concealment, which produces actual ignorance in another generation. A middle-aged lady with an epileptic nephew denied any neurotic antecedents, and was indignant when I told her that three great-aunts had been in asylums; but it was so.

In my own inquiries into the heredity of epilepsy I have limited myself to these two maladies—epilepsy and insanity. I find that in the cases seen in private there is a family history of one or both in 47 per cent., in antecedents and present or past collaterals. The difficulties I have just mentioned justify the assumption that at least 50 per cent., and probably more, really present a family tendency. Among hospital patients the number is not more than 35 per cent., so great a difference does ignorance apparently make. In the facts presented, the percentage was taken from 2,400 cases, of which 600 were seen in private. Heredity was ascertained in 39 per cent. of 1,193 males and 43 per cent. of 1,207 females. These proportions are much less than have been ascertained by others, who have included a larger number of diseases.

It may be well to confine myself to the cases in which a parent suffered. Jeremy Taylor tells us, in one of his sermons, that "an epileptick son doth often come from an epileptick father." Of the total cases in which inheritance was paternal, the father himself suffered in 40 per cent.; when maternal, the mother suffered in only 36 per cent. When epilepsy itself occurred in a parent it was the father who was epileptic in 49 per cent. of the cases and the mother in 51 per cent. ? The cases with insanity in a parent are only one-third the number with parental epilepsy. Of the cases with parental insanity the father was insane in 37 per cent., the mother in 63 per cent. One effect of heredity is to increase the female cases. Where it was absent the excess of males amounted to 4 per cent., but in cases with heredity the same excess was presented by females. This is partly due to the fact that inheritance is more frequently from the mother's side, by 13 per cent., and that the females are in excess by 18 per cent.

The influence of heredity is sometimes strikingly emphasized by the number of sufferers in a family. In one instance six brothers suffered, their mother, two of her sisters, and both her parents. In another, five sisters, five of their children, the mother, her brother's son, and her own mother.

Such facts might be multiplied almost indefinitely regarding many diseases. But your time may be better employed. We are told we are working on an entirely wrong method. Diem states that he has found neuropathic heredity in nearly 70 per cent. of healthy persons. If he has included every conceivable malady that involves the nervous system, it is quite credible but of no significance.

It has been urged that the essential facts for every member of each generation must be recorded to make observations of value, and we are here to-day to profit by a rare opportunity of learning. We have with us those who have devoted keen ability and a vast amount of time to the study of heredity, and we desire to hear from them the way in which useful observations may be made in the complex range of disease, useful to us, and, if it may be, also useful to them.

Professor BATESON, F.R.S.: Mr. President and Gentlemen,—the object, I suppose, that was intended in inviting a layman like myself to speak to a body of professional men on the subject of heredity was that I should tell you something of the results that are obtained in the study of heredity by the application of experimental methods to animals and plants amenable to those methods. The work that we are able to do is accomplished almost entirely by following the hints that we obtained from the work of Mendel, which I suppose, in outline at least, is familiar to almost everyone in the room. I think I shall have no difficulty in showing you that the conclusions to which Mendel came are applicable, in many cases with considerable precision, to the descent of disease or congenital deformity in man. I think it would be wise to begin by a reference to the simplest possible Mendelian case of inheritance, which we represent in the diagram on p. 23. The result of crossing a tall plant (*Pisum*) with a short plant is shown here. The tall is represented by two long lines and the short one by two short lines. We represent our plant by *two* lines because, as every biologist knows, a plant or animal in all the ordinary cases with which we are concerned is a double structure, having received a series of elements from its father and a series of elements also from its mother. The confusion we used to get into when we tried to trace out rules of heredity in animals and plants

was due largely to the fact that we did not realize sufficiently that the plant or animal is a double structure. The *germ-cell* is a single structure, so when we cross our tall plant with our short plant we imagine the meeting together of a germ-cell which is tall with a germ-cell which is short; and we may represent the result diagrammatically by putting them together—a tall line and a short line. It will be known to most of you, I think, that the pea-plant so produced, as a matter of experimental observation, is not of a height intermediate between the tall and the short, but of about the same height as its tall parent. Now, the discovery which Mendel made was, that in all cases to which his rules applied, when dissimilars meet in one individual there is, on formation of the germ-cells, a separation between the two characters which came

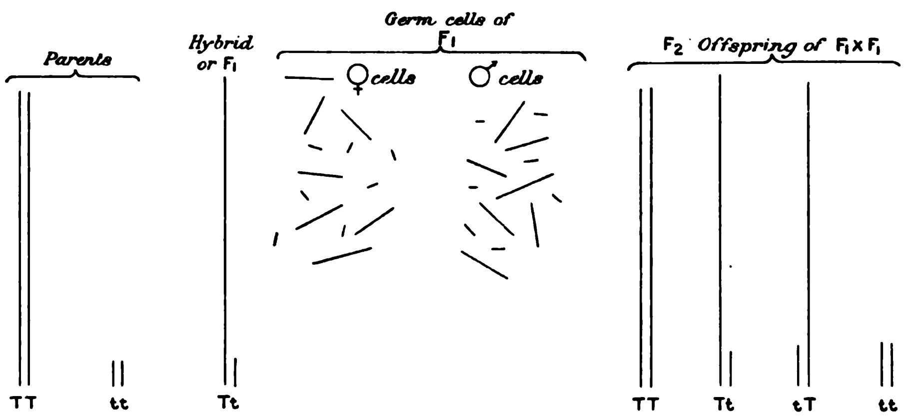


FIG. 1.

A diagrammatic representation of the germ-cells of the tall and short plants, and of their combinations.

in. That may be represented diagrammatically in a crude way by picturing the germ-cells, male and female, as a mixture of long lines and short lines, the long lines representing the germs carrying tallness, and the short lines as the germs destitute of that quality. In ordinary cases the number of each produced is, on an average, equal. That is the phenomenon of *segregation*.

We have been accustomed to talk of the two characters as "dominant" and "recessive," and the terms are useful and applicable. If we consider what is happening to the plant which is made by the union of tall and short germs—why it is tall—I think we are driven to suppose, by examination of a great variety of cases, that its height is due to the introduction into it of some one thing or "factor" from the tall parent,

which factor is absent from the short parent; and that that factor can separate out when the germ-cells are formed, so that some germ-cells possess it and some are without it. The long germs in the diagram possess it and the short ones are without it. The importance of this representation of the dominant as due to a factor present, and the recessive as the condition which results from the absence of that thing, will appear distinctly when I come to speak of the inheritance of disease. The consequence of the combinations of the cells produced by hybrids, females with males, is obviously that in some cases there will be the meeting of long with long, and in some cases the meeting of short with short, and in other cases of short female with short male, or long male with short female. The result will be that where those cells are distributed at random, three of the offspring appear tall and one appears short. The short plants thus reappear because they contain none of the long element. Of the tall plants thus produced some will be pure to tallness, containing two " doses " of the tall factor, others will again be cross-bred, containing only one " dose " of it.

I now put on the screen a photograph which is familiar to many, to show what such a family looks like; they are sweet-peas. These short ones lying on the ground are dwarf plants; they only rise a few inches, while the big ones rise to a height of 5 ft. or more. Here are their tall brothers and sisters, and we know by experiment that the short plants breed pure, just as if they had never come out of the cross at all. They are pure because they have no quality of tallness in them. So some of the talls are pure because they have no shortness in them. The interest of the discovery lies in the fact that it enables us to make analyses of the composition of the animal or plant, in so far as Mendelian principles can be traced. We are able to analyze the plant into its component elements, or, as we call them, units, because they are treated as units when the germ-cells are formed. We must not think of our animal as one thing, but as a combination of a great number of things. The different attributes, such as height, colour, and form, may be, and frequently are, due to distinct factors which are separately transmitted. When we consider the transmission of disease, the application of this principle leads to important results. In a simple case the application of the Mendelian rule to man was traced by Hurst. We know many attempts have been made to discover the descent of eye-colour. The eyes vary in colour between very dark and very light, and it is impossible, by using merely the ordinary names for the colours, properly to define these colours. But

the critical distinction between the dark and the light eye, as Hurst found, turns on whether there is pigment or not on the front of the iris. It is not always easy to see whether the pigment is present or not, but with some trouble it can be made out. The ordinary blue eye is one in which there is no pigment on the front of the iris, while in the brown eye there is pigment on the front. When there is pigment there, it may be transmitted, but when there is none in the parents, the children have none of it. The pigment may be spread over the whole iris, or restricted to some extent, after forming a ring round the pupil. Either type may be pure or impure in respect of eye-colour. The presence of the pigment is a dominant. If a parent is pure dominant, all the children will have colour in the iris; if one parent is impure in the character and the other parent devoid of pigment in the iris, then on an average half the children will have eyes thus pigmented and half have "blue" eyes. Examples of some of these possible matings are shown in the diagrams copied from Hurst (fig. 2, *see* p. 26). One of these shows that a woman who has no colour in her iris, married to a man also without colour, was unable to transmit the colour to children, though her father had colour in his iris. Hurst examined 101 children of such parents, and all were without the pigment. These simple rules so far have been studied only on a small scale. Hurst traced them amongst the people in his own village in Leicestershire, and not until they have been followed out on a larger scale can it be stated with confidence that no exception can be found to them.

Professor Bateson proceeded to show that similar rules can frequently be traced in the descent of certain human diseases and defects. In illustration he exhibited pedigrees of brachydactyly (after Farabee and Drinkwater), remarking that in the three instances in which the descent of a variation apparently meristic had been followed out the *less divided* condition was found to be a dominant. The other two examples were the abbreviated tail of the Manx cat and the aborted coccyx of the "rumpless" fowl (Davenport). Other similar pedigrees were shown relating to keratosis or tylosis palmarum, epidermolysis bullosa, diabetes insipidus, retinitis pigmentosa, irideremia or coloboma, ectopia lentis, and night-blindness. Several of these were taken from the work of Nettleship and from the collections of Gossage. [Other such pedigrees exist for complete abortion of the fingers, split hand and foot, distichiasis, ptosis, certain œdematous conditions of nervous origin, &c.] For most of the diseases named the rule commonly holds that transmission is through the affected

persons only, though exceptions are not unfrequently recorded which call for further consideration. Many of these exceptions were doubtless genuine and as yet inexplicable, pointing, perhaps, to disturbing effects of other factors. Others were attributable to want of opportunity of observing the parents at the right age. Different diseases were sometimes associated under the same name. In retinitis pig-

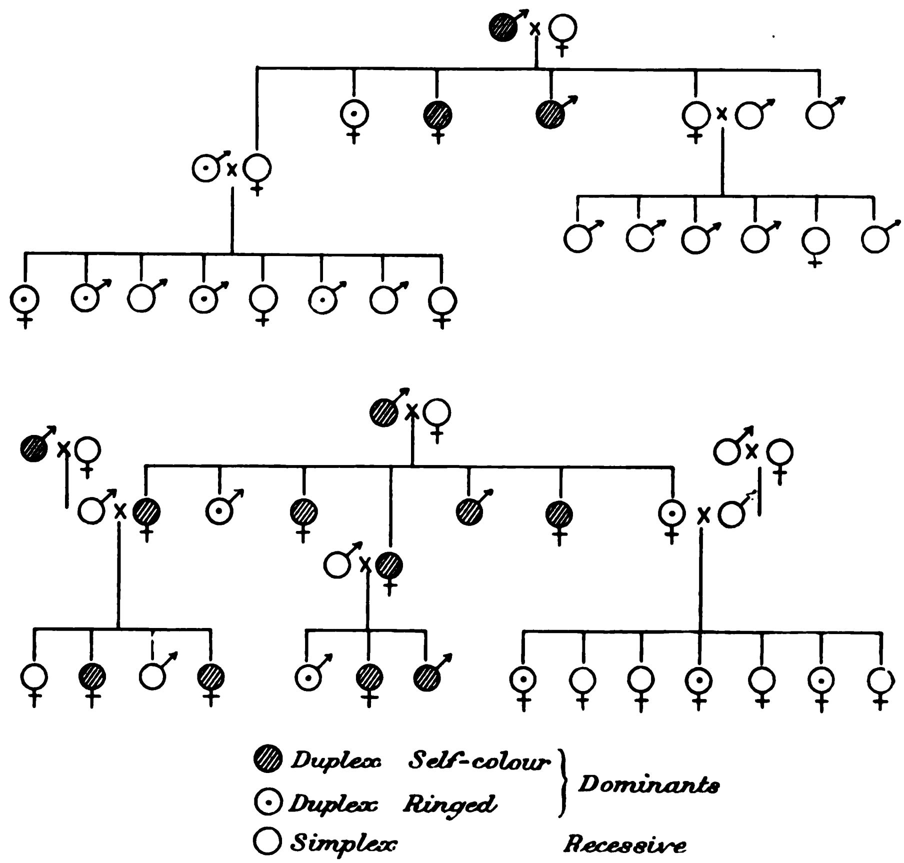


Fig. 2.

Diagrams of descent of eye-colour in two families investigated by Hurst. Copied from *Trans. Leicester Lit. and Phil. Soc.*, 1908, xii, p. 35. See also *Proc. Roy. Soc.*, 80 B, 1908, p. 85.

mentosa, Nettleship's collection of pedigrees showed clearly that the regular descent through the affected was peculiar to certain families. Night-blindness frequently follows the "sex-limited" rule about to be

described; but in the largest pedigree of human defect yet compiled (the work of Nettleship continuing Cunier's materials) the descent had for nine generations followed strictly the rule of transmission through the affected, without exception. Such differences in genetic behaviour probably pointed to differences to pathological nature. As regards numerical results, much irregularity prevailed. Some of the numbers approached fairly closely to the equality expected when cross-bred dominant mates with recessive. Others departed rather widely from expectation. Imperfection of the records was in part, but, he thought, not entirely, responsible for these irregularities, which in some measure he inclined to attribute to physiological causes. In illustration of these numbers the following totals were given. These were of necessity somewhat arbitrarily selected, and for various reasons some families had been rejected. The numbers, however, showed the general course of descent as exhibited by material regarded as homogeneous:—

	Affected	Normal
Brachydactyly (Farabee and Drinkwater) ...	75	65
Abortion of fingers (unpublished)	19	16
Split hand and foot (Lewis and Embleton's collection)	86	64
Cataract, various (selected from Nettleship's collection)	148	155+
Epidermolysis (Gossage's collection) ...	180	209
Keratosis (Gossage's collection)	222	184
Irideremia (various sources)	29	34
Ptosis (various sources)	18	14
Ectopia lentis (various sources)	32	69
Night-blindness (Cunier and Nettleship) ...	130	242[1]
Hereditary chorea (various sources) ...	117	99

[1] Mr. Nettleship gives reasons for believing that the total of normals is here much too high and the number of affected much too low.

There was no reasonable doubt that the descent of these diseases on the whole followed the system of the Mendelian dominant, and that they were due to the presence of special factors, individuals not possessing those factors being unable to transmit them.

As regards tuberculosis, which was due to an infective organism, it was not to be expected that a system of heredity, in the naturalist's sense, should be traceable. The same was not impossibly true in regard to cancer. Special liability to, or special power of resisting, infective diseases might no doubt descend according to Mendelian rules, but no material for testing this in the case of man yet existed.

He continued: The rules for the descent of insanity in general we cannot hope to trace, chiefly because it depends, in so many cases, partly on environmental influences and opportunity for its development. There

is also the difficulty of the diagnosis of different forms, which has not yet been carried sufficiently far for our purpose: we cannot state we are dealing with similar groups. But in hereditary chorea, which is very well defined, it is different. Our numbers are 117 affected, 99 unaffected, which is about as near equality as we can get, or expect to get, in rough data, such as medical records provide.

I have spoken of dominants, and I must now speak of recessives—that is to say, the variations in which something is absent. The albino is an animal which differs from the normal in the absence of something, and, generally speaking, in the case of albinism we have the simplest possible rule which Mendelian analysis can provide. In man albinism is recessive and means that the power of forming pigment is taken out. But in man we cannot get any rule so simple as that which many animals and plants display. These three slides show examples of albinos coming out from normal parents following the converse of that rule which is exhibited by the dominants, and I feel sure that any two of these albinos, if bred together, would have nothing but albino children in all probability. But I have the difficulty exemplified[1] that the number of albinos is far in excess of that which Mendelian rules lead us to expect. I do not think we have evidence sufficient to enable us to discuss the etiology of that.

I should now like to deal with another subject, especially as Sir William Gowers has spoken of it, and that is the descent of sex-limited conditions. The best-known sex-limited conditions are pseudo-hypertrophic muscular paralysis, of which he has spoken, and hæmophilia and colour-blindness. Pseudo-hypertrophic muscular paralysis and hæmophilia are both diseases which are so serious that it is impossible for us to hope to get pedigrees of the descendants of affected persons in sufficient quantity to enable us to investigate them. But colour-blindness is a condition which is not seriously damaging to the chances of

[1] I agree entirely with the remarks subsequently made by Professor Pearson to the effect that the descent of albinism in man is peculiar. As I wrote (*Brain*, 1906, p. 167): "The existence of complication is indicated both by the many degrees in which human albinism may present itself and by the frequent association of the peculiarity with various forms of disease—an association not usual among domesticated animals." Of the slides shown (after Magnus) one exhibited a family from normal parents containing only one normal and *seven albinos*, suggesting a most exceptional behaviour. From various sources I get the totals 197 normals and 126 albinos where the ordinary Mendelian expectation is 242 : 81. Taking all these facts into account, especially the frequency with which albinos have been produced by consanguineous marriage, I think there is no doubt that albinism in man is a Mendelian recessive, but that its descent is complicated by some unascertained disturbance. In the case of alkaptonuria Garrod has shown with great probability that the descent is that of an ordinary recessive. (See especially Garrod, A. E., Croonian Lecture, *Lancet*, July 4, 1908.)

life, and so we can investigate that. The inheritance is well known to be on the lines which Sir William Gowers described, that the sisters of the affected transmitted, or might transmit, to their sons, as, for instance, in a pedigree taken from Nettleship, the affected colour-blind male had a daughter who did not show it, but her son does. The affected, and *sisters* of the affected, transmit.

Now we have been able, I think we may say with confidence, to produce a scheme of descent which represents the facts so closely that there can be no reasonable doubt that we have got very nearly to the actual scheme which is followed by the descent of a simple sex-limited case. I listened with great interest to Sir William Gowers's account of the descent of pseudo-hypertrophic paralysis in the families of those two ladies, and I felt how simply what he said accorded with the principles which we are able to trace by Mendelian analysis. What happens in the descent of sex-limited cases is this. Carry your minds back to the peas. There were peas in which one dose of tallness produces plants of a tall height. There are peas also in which two doses of tallness may be present, but there is no difference in the result. Those that have two doses are tall, and so are those which have one dose. In the descent of colour-blindness there is a difference between these two classes. In the case of females, the female will not be colour-blind unless she has two doses of colour-blindness; she must be *pure* in colour-blindness in order to exhibit it. But the male may show colour-blindness if he has only one dose of it. When the female has only one dose she does not show it, though she may transmit it to her offspring. The colour-blindness is dominant in males, recessive in females. The test of the applicability of these rules is provided by the descent and origin of the colour-blindness in females. According to our rules—to which we are prepared to hear exceptions by-and-by, though they hold so far as we have gone—*the colour-blind female must have had a colour-blind father, and all her sons will be colour-blind.* The normal male has no colour-blindness factor, and will have exclusively normal children unless, of course, his wife introduces the peculiarity. The male who is not colour-blind cannot pass it on, no matter what his ancestry may have been. But the male who is colour-blind can pass it on, and on an average half his sons will be colour-blind and half his daughters will be able to carry on the condition. We have only as yet families of seven colour-blind women available, most of them collected by Mr. Nettleship. They have in all seventeen sons, and all those are colour-blind. We only know the condition of the father of these women in three cases, and in those they are colour-blind.

The importance of this kind of investigation in the physiology of disease is surely this: not only does it enable us to make rules concerning descent (which are liable to all sorts of aberrations owing to various influences), but it gives us an insight into the pathology of these diseases. Colour-blindness, for example, we might have thought was due to the *absence* of something from the body. But from its genetic behaviour we know it is a condition due to the presence of something. It is in all probability due to the presence of some substance which may possibly have an effect somewhat comparable with that produced by nicotine poisoning, producing as this does paralysis of the colour sense.

We have a difficulty in dealing with sex-limited cases other than colour-blindness, that we nearly always find too many persons are affected and too many females carry it on. Herringham's family showing peroneal atrophy is a striking illustration of this difficulty.[1] I cannot yet suggest any real explanation of that discrepancy, and in hæmophilia, where we think we have traced similar rules on these lines, the numbers depart very widely from our expectation. There is, perhaps, a way of dealing even with these exceptions, but I should not be justified yet in suggesting that it is correct. As regards pseudo-hypertrophic muscular paralysis, the pedigrees revealed much irregularity, and it is only in general terms that the descent can be described as following the ordinary sex-limited rule. From a rough tabulation I get the numbers 115 affected, 80 normal where the expectation is equality. When Sir William says no male has been known to carry on the disease I think he must admit we have not yet evidence concerning *affected* males who have lived long enough to have children and show us whether they can transmit it or not. According to our rule, which is not followed with very great accuracy in pseudo-hypertrophic paralysis, the normal males cannot transmit, but abnormal males, if they lived to breed, I think would transmit to their sons.

Dr. G. H. SAVAGE: I feel the responsibility which has been placed upon me, and I feel that it will be difficult in the time allowed to do more than express in general terms my *faith*, which is the result of nearly half a century of experience. First, then, there is a very widely spread feeling that of all the neuroses insanity is the one which is most likely to reappear as the result of parental defect. I at once admit that a very large amount of mental disorder is connected in one way or another with parental weakness; I therefore must admit that some things which

[1] *Brain*, 1889, xi, p. 230.

have been acquired may reappear in the offspring. I shall have, of course, to modify or explain my meaning in detail later. My first difficulty is that the general idea of the passing on of insane tendencies is associated with a feeling of unity in a disease called insanity. This I, of course, need hardly say to those present here has no real ground for reception. Insanity is not a disease, it is only a negation; I shall start by stating, then, that I believe strongly in the power of transmitting from parent to offspring tendencies to mental disorder, but that the transmission is rarely what might be called true. That is, it is not common for the same form of mental disorder to reappear in both parent and child. It is necessary to recognize that there are many branches to the neurotic tree, and that other conditions than heredity may be efficient in developing the form of disorder. I shall hardly have time to do more than state that the offspring of certain insane persons may develop epilepsy, megrim, and moral or criminal faults; or may be simply feeble-minded. I point out that some forms of inherited mental weakness can be looked upon as a reversion to lower types of mind, whereas others are spontaneous variations which are influenced by surroundings and habits of life. As to statistics in reference to insane heredity, I fear I can only say they are very uncertain guides. The patients themselves are ignorant or unwilling witnesses; the friends are unwilling and are also untrustworthy. The dread of *hereditary* weakness is so common that they will give any other reason for the insanity of their relations than a family weakness. This notwithstanding, I give the report of the Commissioners in Lunacy for 1907. Among the private patients 18·6 per cent. of the men and 27·4 per cent. of the women admit hereditary insanity, and of the pauper patients 20·6 per cent. of the men and 25 per cent. of the women have the same tainted history. Of the residents in Earlswood Idiot Asylum, 35·3 per cent. have a bad history, while among the children at the Epileptic School Colony at Lingfield the visiting physician gives 65 per cent., but this he thinks below the truth, as so many of the children are foundlings. The resident medical officer at the Colony goes so far as to look upon hereditary tendency to insanity or epilepsy as almost universal among these children. Dr. Ashby, of Manchester, came to the conclusion that some 75 per cent. of the children sent to special schools belonged to neurotic families.

As I said just now, I believe certain types of mental disorder owe more to hereditary predisposition than do others, and for general purposes I would divide the insanities which I am considering into

those due to neurosis and those due to toxins. There are connecting links, and it is probable that certain of the neurotics are specially liable to be affected by toxins, and it is pretty certain that in many the nervous system, being the most unstable, shows the disorder earliest.

And now as to my experience, rarely is anything like transmission of similar delusions present. When such occur in parent and child one must believe there was contagion by thought and expression. The insane parent may transmit a tendency, as I have said, to any of the various forms of mental disorder, but I must insist strongly on the point that many a neurotic or even insane parent may have sane and even brilliant children. At most it is the few who show the insanity. Occasionally one meets with a family of deaf mutes or of idiots, and in such cases it is not common to be able to trace real insanity in either parent. The union of certain chemical bodies produce bodies totally different from either constituent, and so it is with men and women—variations of very unusual types arise. It is well to recognize that with the insane or the highly neurotic there is such a thing as breeding out the neurosis, and I have seen cases in which the gravest mental disorders in one generation have been represented in later generations by mental tricks, or muscular or moral cranks, and later by simple eccentricities or brilliancy. Here it is well to remark that passing neuroses may be represented by stammering, facial twitches, &c. The danger of transmission is, in my opinion, influenced at times by the sex; thus it is generally thought that the insanity of the mother passes more frequently to the female children, while that of the father passes nearly equally but in a less degree to both. I cannot confirm or deny this from my own experience. I shall later speak of the relationship of certain forms of mental disorder to heredity.

The Commission which recently reported on the feeble-minded and their care devoted much time and attention to the question of hereditary predisposition. They came to the conclusion that feeble-minded parents might have both normal and feeble-minded children, that in many cases the original feeble-minded person was a *reversion*. But their general opinion was that there is a very strong tendency for feeble-minded persons to have feeble-minded children. That bears out my own experience, which is that the more grave and acute forms of mental disorder arising from external causes, such as toxins, are not likely to be reproduced in the next generation, except under very special conditions; for example, the child of a father who has marked general paralysis at the time of the begetting will run great risk of being feeble-minded.

It is supposed that with feeble mind there is a tendency to impaired or reduced fertility; this was not borne out by the Commission, though probably the viability is reduced. A very important question is that of the tendency of certain disorders to skip a generation, and this is certainly met with in the heredity of insanity, though I cannot say that the tendency is very marked unless there is consanguineous marriage or the marriage of a neurotic with a slightly degenerate. It does not seem in my experience common to have a simple skipping. That there may be a latency in a parent I recognize, and I have referred to many unstable children who have been born of mothers who became insane after their birth.

Now as to my experience of transmission of insanity in the concrete. There are certain families in which there lies dormant a most potent power of transmitting tendencies to insanity; I know of several in which every member has had this evil power, and it did not seem to matter with whom they were mated—the offspring were always tainted. In these cases the forms of mental disorder were generally of, either the moral type, so that the patient was a "waster" or a criminal, with uncontrolled passions and lust, or else he was subject to delusional insanity of one form or another. The persecutional cases—those with well-marked hallucinations—have a very general neurotic history. It is interesting to find this because, though these cases come under my neurotic group, these sensory disorders in their acute form are common in the toxic insanities. Organized delusional insanity and forms of moral perversion, then, occur in families in which insanity is common. Next, there is an extraordinary tolerance of acute recurring attacks of insanity in the highly neurotic; I have known a woman belonging to a very insane stock who, during forty years, had more than 100 acute attacks of mania and yet was, in the intervals of health, sane and bright, with no evidence of mental loss. Instability, then, is another of the signs of insane heredity. As already said, though in some cases one may speak of reversion to lower grades in insanity, yet one has to be careful not to make too much of this. As to the transmission of special forms of insanity, I can only say that such forms as seem to depend on some constitutional defect may reappear in succeeding generations. Senile mental changes not infrequently recur in families; I have known a good many instances in which members of certain families died first in brain.

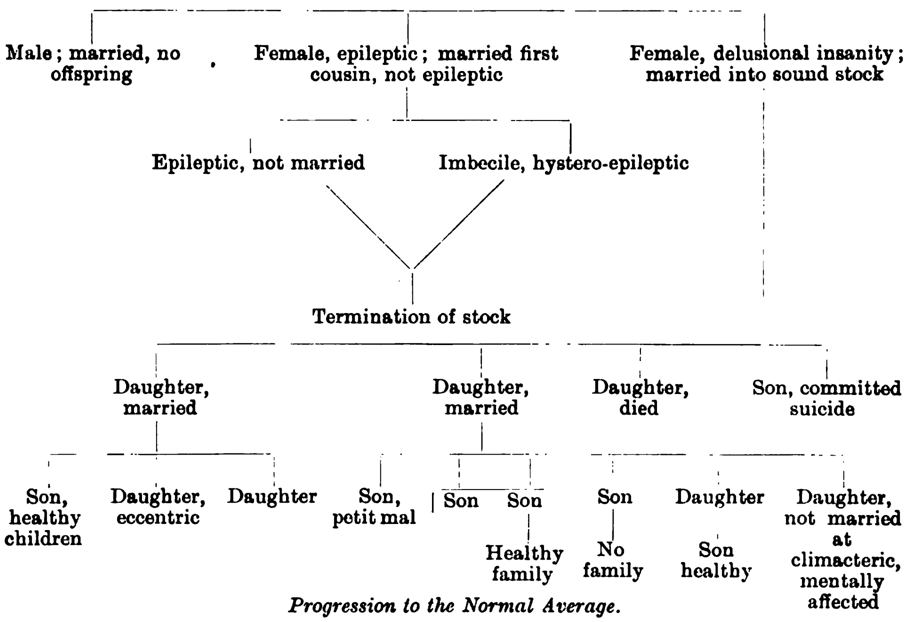
I fear the field I have tried to cultivate is too large for any general utility, but I give my experience, which is, that there is a distinct inheritance of certain mental tendencies; that some of these are

established reversions and tend to persist; that others depend on physical causes; that in some brain defect, which is transmitted and which is also represented in the higher nervous system. Rarely is any definite form of insanity directly passed on, but causes of degeneracy in a parent may lead to feeble mind or mental instability in the offspring—yet from insane stock many healthy children may be born. I cannot altogether pass over what I have called the toxic insanities. First, it is possible that the neurotic are specially liable to exhibit nervous symptoms; when there is fever it is certain that influenza can start a neurosis or may in a neurotic subject precipitate an attack. The chief toxic disease is general paralysis of the insane, and I feel at once the great difficulty here that statistics are almost useless, for though I say that I find a syphilitic origin as the chief factor, there are observers who look upon hereditary predisposition as a very important one, whereas I do not.

Dr. Frederick W. Mott, F.R.S.: When I saw the long list of distinguished men who were to take part in this discussion, I anticipated that I might come on some time after Christmas; therefore I have no precise data to bring before you, although I am engaged in a very interesting research, which I think will have some useful bearing on this question of heredity and disease. Some time ago I was interested to see if the convolutional pattern of the brains of relatives showed any resemblance, such as their physiognomies so often do. I therefore instituted an inquiry with the object of obtaining the names of all the patients related to one another now inmates of the London County asylums. A number of brains of those deceased have been sent, and I have handed them on on to Mr. Edgar Schuster, of Oxford, who is photographing and describing them with a view of ascertaining if there are similarities in the convolutional patterns. When I began the inquiry I sent papers to all the London County asylums, and the returns from some of them showed comparatively few relatives. Further inquiry, however, led to a large increase in the numbers, for many relatives were discovered in the other asylums, and cross references of the returns led to an increasingly long list, so that the number of inmates related to one another is surprisingly large; a big snowball is formed, and is getting larger every day. This is a broad fact of considerable importance in relation to the study of heredity and insanity, because it is often very difficult to obtain histories about these insane people. Many patients are admitted knowing nothing about their relatives, and many are so demented that they can tell you nothing even about themselves. Again,

many patients are not visited by friends. Some are visited by friends, but they so resemble the inmates that one thinks of one having been taken and the other left. Sometimes the only history to be obtained is that the patient has had fits; yet among related patients I have met with a few very remarkable family histories. It is as a rule, however, in these family histories impossible to trace any one form of insanity (fig. 1).

SHOWING THE EFFECT OF A NEUROPATHIC STOCK MARRYING INTO A SOUND AND NEUROPATHIC STOCK.



Progression to the Normal Average.

FIG. 1.

I have, however, met with an example of four generations of suicides, associated with insanity in the other members of the stock, so that nearly all the members of the family were insane (*vide* fig. 4). I have recorded an instance of a drunken father whose children were nearly all insane, and this has been copied into temperance books; but beneath this family tree I put another of two parents who were total abstainers, yet all their three children suffer from adolescent insanity; they were neither of them insane, but there was collateral insanity on each side (*vide* figs. 2 and 3). I have every reason to believe that careful investigations of the family histories of some of these insane relations in the London County asylums will show many interesting facts concerning the inheritance of an insane temperament, and I hope later on to be able

to present statistics with regard to the same. I have collected already many hundreds of related inmates in the London asylums; there are certain types of insanity which are especially noticeable; they are imbecility, delusional insanity, adolescent insanity (dementia præcox), manic-depressive insanity, and recurrent insanity. These last-named cases make up a considerable percentage of the cures, for they come in, get better, and are discharged, to be subsequently readmitted, after having possibly reproduced their species. They are not, in the ordinary sense of the term, anti-social, and so they are considered cured. There is nearly always an hereditary taint in these recurrent cases.

Sister insane — Sister insane

Father — Mother (both total abstainers)

Daughter; dementia præcox, Claybury Asylum	Daughter; dementia præcox, Bexley Asylum	Son; dementia præcox, Hanwell Asylum

FIG. 2.

Father, born 1830; no family history of insanity, fits, or nervous disease; chronic drunkard from boyhood; in asylum from June 12, 1876, to July 11, 1876, and from January 19, 1892, to February 8, 1892 — Mother; no history of insanity in family

Daughter, born 1859, admitted to asylum Oct. 24, 1874; discharged and re-admitted on subsequent occasions; still in asylum	Daughter, born 1860, admitted to asylum Oct. 6, 1874; discharged and re-admitted on subsequent occasions; still in asylum	Son, born 1862, admitted to asylum June 29, 1877; discharged and re-admitted and discharged on two subsequent occasions	Daughter, born 1869, admitted to asylum Jan. 2, 1892; discharged and re-admitted; still in asylum	Son, born 1872, admitted to asylum Nov. 24, 1888; died of tuberculosis Sept. 4, 1902	Son	Daughter	Daughter
					$\underbrace{\text{Not been in asylums}}$		

FIG. 3.

General paralysis of the insane so far does not prove common among relatives; I have only found a few cases in each hundred, and in those there has often been general paralysis in a parent—usually the father—and in a daughter or son, in whom also we frequently find signs of

hereditary syphilis. In every juvenile general paralytic case I have investigated I have obtained a history which is conformable with congenital syphilis. The question why general paralytics so seldom exhibit signs of syphilis on the body is one of great interest, and I think it shows that when syphilis affects a whole race there is acquired a widespread tendency to immunity, but that it is at the expense of the cells of the body throwing out antibodies to neutralize the effect of the syphilitic virus. Recent investigations of Wassermann and others, who have found antibodies in the cerebrospinal fluid and blood-serum of general paralytics in practically nearly every case, suggests that the nervous system undergoes decay and wears itself out in throwing out these antibodies to neutralize the effect of the conditions produced by the virus of syphilis.

Another very important matter which arises from these researches, and in regard to which I hope soon to give more precise data, is the relation of tuberculosis to insanity. It seems to me that tuberculosis is not acquired in asylums to such an extent as is commonly believed. I have gone into this point fully; it is a question of the soil and the seed, and I am not sure that the soil is not just as important as the seed. Patients admitted to asylums are of low vitality; they readily acquire tuberculosis; and the onset of tuberculosis may coincide with the development of the insanity, both being due to a depression of the vital functions of the body; only in the insane, as distinguished from the sane, the brain shares in the nutritional failure.

I have records of more than 2,000 consecutive necropsies, and I find that in the first three or four decades certain types of insanity are particularly prone to tuberculosis—*e.g.*, adolescent insanity, melancholia, and imbecility. I do not think there is a tuberculous insanity, as Professor Clouston used to teach, but I believe there is a soil which leads to the easy development of the tubercle organism. The subjects become melancholic and stuporose, so that you can understand that it may be difficult to diagnose the disease by the physical signs. The tubercular incidence at the same ages is from ten to fifteen times as great inside asylums as it is outside.

Comparison of Tubercle Death-rates per 1,000 living, Sane and Insane.

15 to 19 years,	insane	17	times as great	as sane
20 ,, 24 ,,	,,	14	,,	,,
25 ,, 34 ,,	,,	13	,,	,,
35 ,, 44 ,,	,,	6	,,	,,
45 ,, 54 ,,	,,	2	,,	,,
55 ,, 64 ,,	,,	3	,,	,,
65 years and over	,,	4	,,	,,
Total average ...	,,	8	,,	,,

These figures have been obtained from Sir Shirley Murphy's data and those derived from the returns of the London County asylums for 1907. From the asylums only those cases of tuberculosis in which the disease was the cause of death are included. If the figures for the sane above 45 years of age were based on post-mortem examinations, as are the insane, it is a question whether there would be much difference.

It is not, I believe, that the air of asylums is bad; I do not believe that it is so, because attendants who are practically all day long in the wards are hardly ever affected; and when they are, it is seldom that there is not a history of tuberculosis in their family. Of course, it is possible that patients, although they are examined on admission and no tubercle discovered, nevertheless may have had latent tuberculosis; and this may account for a good few of the cases which develop tuberculosis of an active recognizable form within a few months to a few years of admission. Moreover, post-mortem observations clearly show facts indicating the probability of the existence of tubercle, obsolescent or active, in a large number of cases before admission. Another important fact with regard to tuberculosis is that I have not found a single case of tubercular meningitis among the very large number of autopsies which I have made. Tuberculous ulceration of the intestine occurs, however, in one-third to one-half the cases.

Now, in regard to alcoholism. It is said that alcohol is the most important cause of insanity. I would not for a moment say it is not a most important exciting cause of insanity in persons with an insane temperament, but from a large series of post-mortems at Claybury—I have made 2,000 there—I have only once seen a case of cirrhosis of the liver with ascites, and that was in Jane Cakebread, who was convicted 400 times before she was found to be incapable of taking care of herself. If alcohol be such an important cause, it is not shown in a marked degree in the organs. However, alcohol acts as a poison to the epileptic or the potential lunatic and brings him into the asylum very much sooner than it would an ordinary individual. In a long series of investigations which I made upon cases admitted to the asylums in which alcohol was the assigned cause, I found an hereditary history of insanity in the family as frequently as in other patients with no alcoholic history.

Heredity and Suicide.—The actuaries, from long experience, have found it necessary either to refuse a life in which there is a strong family history of suicide or to increase the premium considerably. Not only have numerous instances been recorded of members of a family for

several generations committing suicide at the same period of life, but in an identical manner. Of course, such episodic phenomena may be the result of imitative suggestion on the members of a neuropathic stock. I will throw on the screen an example of such which occurred at Cane Hill Asylum. As a rule, however, no particular form of insanity is hereditarily transmitted, but only a tendency to mental instability, which manifests itself in various and manifold ways. It is therefore necessary, in any careful statistics, to learn whether any members of the family have suffered with neurasthenia, hysteria, epilepsy, petit mal, migraine, chorea, insanity of any kind, or suicide. Residence in an asylum, in the majority of instances, would mean a neuropathic tendency, but not necessarily, any more than the fact of a patient not having been in an asylum does not necessarily mean that a patient has not been insane. The more care that is taken in going thoroughly into the history of the stock, direct and collateral, the more convincing will be the evidence of the importance of heredity in the production of all diseases, but especially of tuberculosis, rheumatism, gout, and nervous and mental diseases.

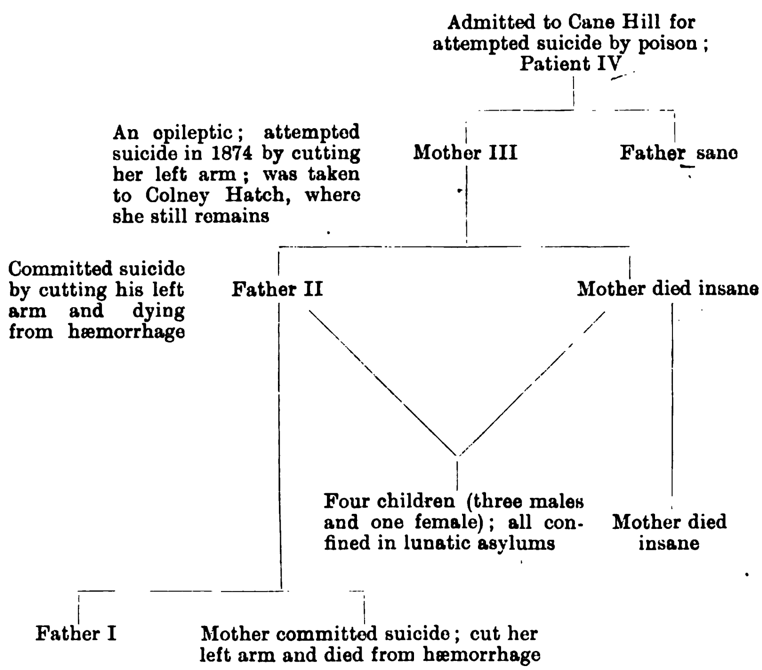


FIG. 4.

Dr. MERCIER[1]: The influence of heredity on disease, especially disease of the nervous system, may be approached from several aspects. I propose to confine myself to pointing out some of the fallacies by which the subject is beset, and to indicating some of the precautions that ought to be taken to avoid these fallacies. The usual mode of determining the existence of an hereditary propensity to a disease is to ascertain whether there are, in the parentage or ancestry, or among the near relatives of the diseased person, instances of the same disease; and, if such instances are found, to conclude that he derives his disease by inheritance. Such a method is utterly fallacious, unless hedged about by precautions. The fallacies to which it is open are many. The most obvious trap is in the application of the method to diseases of frequent occurrence. Supposing a disease so common that it affects nineteen-twentieths of the population, then nine out of every ten persons will have both parents affected by it, and only one person in 360 will have both parents free from the disease. Such a large percentage of parental disease would justify, according to the method in use, the conclusion that the disease was certainly and strongly hereditary; and thus we should arrive at the conclusion that a common cold is an hereditary disease.

It is very frequently argued that insanity is an hereditary disease because persons who are insane, or who exhibit nervous instability in other ways, are frequent in the families of the insane. But until very recently no attempt whatever has been made to ascertain whether such persons are not as frequent, or even more frequent, in the families of the sane. The various manifestations of what we will call for the moment "nervous instability" are so extremely common, that it is quite unjustifiable to draw, from their frequency in the families of the insane, any inference as to the heritability of insanity. For my part, I am constantly impressed with the number of insane persons (not including general paralytics) in whose families exhaustive search fails to discover any insane relative within a reasonable degree of consanguinity, and I am almost more impressed by the number of sane and normal persons who possess near relatives that are either insane or subject to allied nervous disorder. When we are confronted with the percentage of insane persons among whose near relatives insanity is known to exist, we cannot fail to be impressed with two remarkable facts: first, how relatively small this percentage is; and second, that the statistics, even if taken at their face value, do not even purport to be anything but an

[1] Dr. Mercier reopened the discussion on November 18.

enumeratio simplex, and cannot be made the basis of any valid conclusion until they are compared with similar statistics of the percentage of insane relatives among the sane. This source of fallacy is less apt to be present in the case of rare than of common diseases. When a comparatively rare disease, such as hæmophilia, or pseudo-hypertrophic paralysis, or tylosis, or any of the others adduced by Professor Bateson, is found to exist in the parents or other near relatives of the diseased person, such a distribution of the disease is usually regarded as conclusive proof that the disease is hereditary. The inference is quite unwarrantable, and is usually shown to be unwarrantable whenever we discover the cause of the disease. A disease may be limited to a certain family or families without heredity having anything at all to do with the limitation. It may be heritable or it may not, but we are not justified in concluding that it is heritable merely because it exhibits family limitations.

It is quite conceivable that a father and sons might come to this country, all suffering from filariasis or sleeping sickness, but we should be led widely astray if we concluded, from the family limitation of the disease, that it was heritable, and that the sons had derived it from the father—they might all have derived it from a common source. Or a mother and daughters might be found all suffering from leprosy, and yet we should not be justified in concluding that the daughters derived the leprosy by inheritance from the mother. These instances are so flagrant that they are not likely now to lead to mistake, and mistake is unlikely because we now know the causes of these diseases; but it does not follow that mistake has not been made, may not yet be made, and is not now being made, in cases in which the cause of the disease is obscure. And the cause of insanity is still obscure. If father and son were both afflicted at about the same age with general paralysis of the insane, we should not, with our present knowledge, ascribe the insanity of the son to inheritance from the father; but twenty years ago we should certainly have drawn this inference, although, in fact, the son might have been begotten before the father acquired syphilis. Even at this day, insanity is ascribed to inheritance on no better ground than its occurrence in several members of one family, and, I repeat, the cause of insanity is still obscure.

We have not yet by any means exhausted the fallacies of the *argumentum per enumerationem simplicem*. Even if we can establish beyond question and beyond cavil that the disease falls with special virulence upon certain families, generation after generation, and leaves unaffected other families whose circumstances are, to all appearance,

practically the same; even if we can establish that the members of families so affected have certain stigmata or distinguishing marks by which they can be recognized as liable to the disease, still we are not justified in any conclusive presumption that the disease is heritable. All that we are justified in concluding is, that it is probable that inheritance plays a part in its production. Something contributing to the disease must be inherited in such cases, but it does not follow that what is inherited is the disease itself. It may be a special vulnerability of tissue or a special quality of blood, which renders the person so inheriting unable to resist the attacks of the noxious agent which is the true cause of the disease. This is the part played by inheritance in tuberculosis, and this is the explanation of that apparent heritability of phthisis which deceived our predecessors. Inheritance may play an important part in the production of tuberculosis, but tuberculosis is not inherited. I believe that the apparent heritability of insanity is often of the same nature.

For all these reasons I submit that we are apt to talk a little too glibly about the inheritance of diseases, of physical inefficiency, of feeble-mindedness, and of what some people are pleased to call degeneracy, whatever that may mean. It appears to me that when we deal with the inheritance of disease, we are apt to relax the rigid canons of scientific inquiry, and to admit evidence that would be scouted in the laboratory for lack of those "controls" which alone can give validity to observations. Supposing, however, that we have guarded ourselves against all these sources of fallacy, and are justified in concluding that a disease is indisputably inherited, then we have to estimate the significance of that conclusion, and the significance, for the members of the family in which the disease occurs, will differ immensely, according to whether the disease is merely a variation, or whether it is a true mutation. If it is a mere variation—if, that is to say, it is a more pronounced deficiency or excess of some quality which generally varies in quantity—then it has little significance as a racial peculiarity. Such variations have a strong tendency to return to the average. Unless they are artificially cultivated by the pairing of individuals of like variations, such qualities return to the average in a few generations. The variation is soon bred out. Such variations are giantism and dwarfism on the physical side; on the mental side, brilliant ability and feeble-mindedness; and there are many other variations of like nature. Each of them is the exaggerated excess or defect of a quality, which is generally in some degree excessive or defective when compared with the average, which

presents in different persons an indefinite number of degrees above the mean, and an indefinite number of degrees below. Scarcely any one is of precisely average stature or of precisely average intelligence. Children usually differ from their parents both in stature and in intelligence. Numbers of persons are exceptionally tall, numbers exceptionally short; numbers are exceptionally clever, numbers exceptionally dull. Every now and then appears a giant or a dwarf; every now and then a person of brilliant ability or a person of feeble mind. When variations like these occur, we know that they will scarcely ever be propagated in full force, even if they exist in both parents; and we know that they will not attain to any considerable degree of fixity in the race, unless both parents have been selected for several generations for the exceptional degree in which they possess these qualities. Such variations are difficult to fix, easy to breed out, and give us little anxiety about the future of the family in which they occur.

It is otherwise when the quality is not a mere exaggeration of a frequent variation, but a true mutation in the sense of de Vries—that is to say, a quality appearing *de novo* in the race. Then it will breed true. Then it will appear in an indefinite number of generations of the descendants of the person in whom it first appeared. It will appear in an indefinite number of generations, but it will not necessarily appear in each individual of each generation. Its appearance in successive generations will be governed by the laws of Mendel; and it is in such cases only that we are warranted in speaking of a true inheritance of disease. Whenever a disease is distributed in successive generations in accordance with Mendelian law, we cannot doubt that the disease is truly inherited; but we are not entitled to assume the converse, and to limit the inheritance of disease to those instances in which the numerical proportions required by the laws of Mendel are strictly observed. In the first place, it is probable that there are disturbing factors which interfere with strict numerical accuracy. In the second place, it is manifest that the number of offspring of any one pair of human beings is too small to allow the law of Mendel to assert itself completely. Mendel's law resembles the law of Probability, of which it is in fact a simple case, in never being strictly true except "in the long run"—that is to say, when applied to an infinite series. And the series never is infinite. The run is never long. In the human race it is a very short run, and therefore the law never can be strictly true except by accident. But it always tends towards truth, and, other things being equal, it will be the more nearly true the larger the numbers to which

it is applied. Its approach to truth may be plotted as an asymptotic curve, and to flout it, as some of its critics do, because it is scarcely ever accurately true, and is often wide of the truth when small numbers are dealt with, is to misconceive its nature.

Inheritance of diseases of the nervous system is particularly important in the light that it may be expected to throw upon the vexed question of the inheritance of acquired qualities. The nervous system is literally the creature of habit, and it seems to be beyond doubt that habits may, on the one hand, be acquired, and, on the other, inherited. The dog's habit of turning round before he lies down is a case in point. If such orderly habits can be transmitted, then it seems that such a disorderly habit as epilepsy may be transmitted. There is evidence that epilepsy occurs in the families of epileptics more frequently than it would if it were evenly distributed over the population; and yet it has not been observed to be distributed in successive generations in accordance with Mendel's law. Until we find it so distributed, we must regard it either as a variation, and therefore tending to be bred out in succeeding generations, or as a quality acquired under the influence of some circumstance in the surroundings, and therefore not strongly heritable from the first generation. We cannot regard it as a true mutation which will inevitably appear again and again in successive generations. It is clear that if Mendelism assists us to determine a matter of such vast importance as this, it is worthy of the closest attention and study. Meanwhile its great value is that it indicates to us what we ought to look for, what facts are to be observed, and does not leave us to the random application of the *argumentum per enumerationem simplicem*.

Of the inheritance of insanity I speak with the greatest diffidence, for, in spite of the collection of statistics over many years, their value is so impaired by the fallacies already enumerated, as well as by the difficulty of obtaining evidence either trustworthy or complete, that it would be very dangerous to draw any deductions from them. In compiling these statistics, regard has been paid solely to ascertaining the existence of other cases of insanity in the families of the insane, and if any such case is found, it is put down in the table as "hereditary influence ascertained." That is to say, an unjustifiable inference has been founded upon a fact, itself often doubtful, and this inference has been stated as a fact of observation.

There has been no attempt to record the number of cases of insanity in any family, far less has there been any attempt to estimate the number of the sane members, and to compare the sane and the insane numerically. The compilation of the statistics of inheritance which

appear year after year in the Reports of the Commissioners in Lunacy is a gigantic waste of time and labour. The statistics are of no value at all for any practical or scientific purpose. As far as my own observations of the family history of the insane go, they seem to show that, in some families, the insane members are distributed approximately in accordance with Mendelian rules, and in some they are not. In some cases insanity seems to appear *de novo*, as a mutation, in families in which it has not appeared before. In others it is clearly a variation—an exaggeration of a normally variable quality. In the former case, we see families in which insane members exist side by side with others who are thoroughly sane; in the latter we see all the members of the family exhibiting various degrees of unsoundness. I am convinced, moreover, that in some cases of family insanity the heritable quality is not insanity itself, but a special liability either to the production of toxins or to the action of toxins on the brain.

It is clear that if our investigations into the influence of heredity on insanity are not to be as barren in the future as they have been in the past, our methods must be entirely remodelled. Not only must we guard against the fallacies I have indicated, not only must we cease to posit untrustworthy inferences as observed facts, but the facts collected must include not only the existence of other cases of insanity in the families of the insane; not only a numerical record of these instances; but, in addition, a numerical record of the sane members of such families, and numerical records of both the sane and the insane members of the families of the sane. When these data have been collected on a large scale, then, and not until then, shall we begin to be able to draw trustworthy conclusions as to the influence of heredity on insanity.

Dr. Arthur Latham[1]: Our knowledge on the influence of heredity upon tuberculosis is not precise. We can do little more than state certain more or less well-established facts and suggest possibilities. We know that the transmission of the tubercle bacillus from parent to child *in utero* is more common than was at one time supposed, but that it is so rare that it is a negligible factor. Certainly the number of instances in which there is clinical evidence of tuberculosis at birth is small. Thus, Schleuter in 1902 only succeeded in collecting twelve well-authenticated cases in man and seventy in animals. The theory that the children of tuberculous parents are born with tubercle bacilli within their bodies, and that these remain latent for years, is unsupported

[1] Dr. Latham opened the discussion with regard to tuberculosis.

by evidence. It is in all probability true that several years may elapse between the date of infection and the appearance of definite clinical signs or symptoms, but it is impossible to prove that such infection took place before birth and not afterwards. We find that in the great majority of instances the organs of fœtuses born of tuberculous mothers give negative results when inoculated into guinea-pigs. If we neglect the rare instances of the hereditary transmission of the germ, what view are we to take of the theory that the soil is transmitted, that there is an hereditary transmission of predisposition, constitution, or diathesis from tuberculous ancestors to their descendants? Modern knowledge has made such a theory less and less probable, for it is becoming clearer that the dominating factor in the incidence of tuberculosis is the opportunity for infection. We know of no instance of a naturally refractory animal or of an artificially immunized animal which is proof against infection by a sufficiently large dose of a sufficiently virulent strain of tubercle bacilli. Clinical experience leads us to the same conclusion in man. A general review of our knowledge shows that the greater the opportunities for infection the greater is the incidence and mortality of tuberculosis. It is difficult to give clear evidence of this, for the effect of environment cannot be wholly eliminated. Environment, however, merely acts by lowering the vitality, and so makes a smaller dose of bacilli effective and diminishes the immunizing capacity of the individual. The differing incidence of tuberculosis in different trades and in clean houses as against similar but dirty houses are suggestive of the part played by infection. So, too, are Cornet's investigations upon the death-rate from tuberculosis among certain religious orders devoted to nursing. In a review of thirty-eight cloisters embracing the average number of 4,028 residents, there were 2,099 deaths in twenty-five years. Of these no fewer than 63 per cent. were due to tuberculosis. Conversely, we know that by limiting the opportunities for infection we can practically limit the incidence of the disease. Bang's classical experiment proves this. This observer isolated the calves born in a tuberculous herd, and in this way was able to establish a herd which was free from tuberculosis. The same thing is shown by the effect produced by active preventive measures in man. Of recent years more active preventive measures have been adopted in New York City than in other great towns. As a result there has been a more rapid fall in the tuberculous death-rate in New York than in any great city in the world, and, what is of interest to this discussion, there has been a decrease of 40 per cent. in the death-rate in children aged under 15

from pulmonary tuberculosis and tuberculous meningitis during the last ten years, notwithstanding the extraordinary difficulties—chiefly due to the immigrants—present in New York.

We know that infection can always be effective, no matter what the man's diathesis is, under certain circumstances. We also know that in animals and in man the capacity for resistance differs in different individuals. Whether this difference of capacity for resistance depends on inherited characteristics or not in some instances, we know that whatever the resistance of a man may be to start with, it can be profoundly modified by various agencies. It is an established fact that a high mortality from tuberculosis in any community is always associated with imperfect sanitary conditions. Again, anything which leads to malnutrition leads to a lowered resistance, and, in consequence, an increased mortality from tuberculosis. This is shown by the increase of tuberculosis which is associated with widespread unemployment and with overcrowded poor districts. Chronic diseases which are characterized by loss of nutritive capacity are stated to be associated with an excessive percentage of tuberculosis. Thus the incidence of tuberculosis is excessive in the insane, and the death-rate from pulmonary tuberculosis in young persons suffering from diabetes is stated to be greater than it is in non-diabetic persons of the same age. The influence of environment or disease would appear to act chiefly by lessening the resistance to infection and to be perhaps chiefly important in its effect upon the course of the disease. Environment in its most comprehensive term lessens the resistance to the disease, and hence it causes a greater number of persons to become victims of the ubiquitous infection. More important still, it reduces the immunizing capacity of these victims, and hence persons who, under better conditions, would have acquired a partial immunity and so have been cured of the disease fail to get well, and by acting as carriers of the infective material lead to an increased incidence of tuberculosis. The influence of environment on the course of the disease was well demonstrated by Trudeau, who found that rabbits inoculated with tuberculosis rapidly died if they were kept in a dark damp place, whilst others inoculated in the same way but allowed to run wild usually recovered. Similarly it is stated that efficient drainage of the soil at Salisbury, Ely, and Rugby was at once followed by a reduction in the mortality of pulmonary tuberculosis of 49 per cent., 47 per cent., and 43 per cent. respectively.

The part played by infection and by environment are important when we come to the question whether persons who suffer from tuberculosis

transmit a predisposition to this disease, because it is impossible to say whether these two factors have been given their true value in the various investigations made on this subject. Formerly the medical profession were convinced that a tuberculous taint was transmitted from one generation to another. At the present time our opinions are less dogmatic. If we look at infective disease as a whole we find little evidence on which to base the opinion that predisposition to infective disease is transmitted from parent to child. In syphilis it is true that the disease is transmitted in certain instances to the next generation. Such transmission is less frequent according as the parent has been adequately treated—that is, it varies directly with the degree of immunity acquired by the parent. Further, just as congenital cases of tuberculosis are due to the direct transmission of the tubercle bacillus, congenital syphilis is due to the direct transmission of the *Spirochæta pallida*. Lastly, inherited syphilis in the third generation is not an accepted fact. Those who hold that there is an hereditary predisposition to tuberculosis base their opinion largely, if not wholly, on statistics which purport to show the incidence of the disease—and chiefly of only one clinical form of the disease—in families of a tainted stock as compared with its incidence in families of an untainted stock. Several objections, apart from the difficulty of excluding the influence of greater opportunities for infection and the influence of environment, may be brought forward to show that such statistics are probably misleading.

(1) These statistics are nearly all based on comparatively small figures. It is probably owing to this fact that the estimates given by different authors vary greatly. Thus the estimates of the number of persons who have an hereditary predisposition to tuberculosis is variously given as being from 10 per cent. to 80 per cent. of the general community.

(2) The statistics are based on answers obtained from individuals as to the cause of death or the occurrence of tuberculosis in their ancestors and relatives. In most investigations the answers given by uneducated people are accepted with little reserve. Hospital experience has shown us that such data are quite unreliable in the lower middle and poorer classes. An insurance experience which brings nearly 4,000 family histories annually before my notice has convinced me that even intelligent members of the upper classes are strangely ignorant of the disease-history of their families, and that their statements as to the cause of death are frequently unsubstantiated by further investigation. Most medical men will agree with me when I assert that statistics as to the

incidence of tuberculosis which are based on the statements of relatives are absolutely unreliable.

(3) Most of the family histories collected on this hearsay evidence are incomplete. In nearly all investigations children or others whose life-history is not at an end are included. In view of the fact that there is good clinical evidence to suggest that infection may occur and yet not give rise to the clinical symptoms of the disease for some years, it is clear that if we are to have a complete picture we must have completed family histories.

(4) These statistics are all confined to the influence of one example of tuberculosis—namely, the pulmonary form—and in most, all reference to the occurrence of tuberculosis of the glands, bones, joints, testicles, peritoneum, &c., is omitted. Recent research has shown that the organ or tissue which may happen to be infected is largely a matter of chance, which is determined chiefly by the portal of infection and partly by the age of the affected person. The differences due to the age of the affected person would appear to be dependent in part upon the distribution and arrangement of the lymphatic system at various periods of life. The transmission of any defective resistance to tuberculosis is probably independent of the fact whether we are dealing with pulmonary or bone tuberculosis, for it is no uncommon thing to find three or four different forms of tuberculosis in one and the same family. It has become clear that if we are to have clean evidence on the subject of the transmission of an hereditary predisposition in this disease we must not confine our attention to examples of pulmonary tuberculosis, but must embrace all forms of tuberculosis in our inquiries, more especially when we remember that all the various forms are capable of producing, and eventually often do produce, the pulmonary form in their host.

(5) The statistical investigations are confined to tuberculosis which has been associated with definite clinical signs, and no differentiation has been made between persons who have become cured, and have therefore acquired a partial immunity, and those who have been unable to make any effective resistance to the disease. Further, all reference has been omitted to cases of pulmonary tuberculosis which have become spontaneously healed (cases, that is, in which a partial immunity has been acquired) without showing any evidence of the disease during life. How frequently tuberculosis undergoes a spontaneous cure, and in a large proportion of cases without ever having been detected during life, is shown by pathological records. It is generally allowed that there is evidence at death of tuberculosis having occurred in at least 30 per cent.

to 50 per cent. of the community, and that the proportion increases with age—that is, as the risks of infection increase. Some authors go further, and many of us will be inclined to agree with them; thus Naegeli found evidence of tuberculosis in 97 per cent. of 500 consecutive autopsies, and Osler has stated that if a systematic laboratory investigation is made tuberculous lesions are found in practically 100 per cent. of adult bodies. It is highly probable that persons who have acquired a partial immunity and have overcome the infection and persons who are unable to acquire any real immunity or to offer real resistance to the disease have different effects on their descendants. It is possible that one might represent the long plants which have been investigated by Mendel, and the other the short plants.

It is clear to my mind that statistics which are based largely on old wives' recollections, on uncompleted family records, on a selected form of the disease, and in which no reference is made to the fact whether any immunity has been acquired or not, cannot give us a scientific insight into the question of an hereditary predisposition. It is also clear that any statistical investigation, if it is to be scientific and not futile, must be based on adequate post-mortem records of the grandparents, and parents, and every member of the family.

If we consider the statistics which are based on family histories, and to the value of which I have brought forward the above objections, what do we find? Dr. Shrubsall, who has investigated the records of the Brompton Hospital, will tell you that it is difficult to arrive at any definite conclusion. Professor Karl Pearson's investigation, which is perhaps the most recent and careful one, but which has many of the faults to which I have alluded, is based on between 200 and 300 fairly complete family histories. Professor Pearson holds that his figures show that 50 per cent. of the offspring of tuberculous parents become affected with tuberculosis, and adds that he is inclined to think that the theory of infection does not account for the facts, and that constitution or diathesis means almost everything for the individual whose life cannot be spent in self-protection. If we allow that 50 per cent. of the offspring of those suffering from pulmonary tuberculosis eventually suffer from this form of the disease owing to their inherited want of resistance, we should, I think, expect a progressive increase in the total incidence of the disease and a progressive increase in the total mortality in this country, provided we bear in mind the increase of population. Now, what do we find? Pathological evidence shows that most of us have sufficient resistance power to overcome the infection. In spite of the fact that all of us are

infected the statistics of this country show that each decade we are more able to resist the disease. The Registrar-General's statistics show that the total annual deaths from pulmonary consumption have fallen from 59,005 in 1838 to 39,746 in 1906, in spite of the enormous increase of the population during that period, and that the death-rate from this disease per 10,000 living has been reduced during that period from 38·8 to 11·5. The factors of immigration and emigration cannot have affected these figures, for tuberculosis is an almost universal disease, and the incidence in England and Wales is less than in most countries. It might be that this enormous decline depended on the comparatively early death-rate of consumptives and their lessened capability for producing children, but we find that from 1851 to the present time the age of maximum mortality from pulmonary tuberculosis has risen in males from between 20 and 25 to between 45 and 55, and in females from between 25 and 35 to between 35 and 45, and that therefore the capacity for consumptives to produce families and to transmit the predisposition, if it exists, has been very largely increased.

It is difficult to correlate these facts, which are based on large and probably fairly correct figures, with the assumption that an inherited predisposition to consumption is transmitted from one generation to another. They certainly suggest that further investigation of a more scientific kind is required before we can usefully draw conclusions from the statistical investigations which purport to show that there is an inherited predisposition to this disease. It is difficult to account for the progressive fall in the incidence of consumption. Still, it is worth while to make the attempt. Dr. Bulstrode has shown that the fall has been gradual and continuous. He has further shown that such things as the Public Health Act of 1875, the discovery of the tubercle bacillus, the Housing of the Working Classes Act, and the commencement of notification and sanatorium treatment have produced no immediate or unusual fall. There can be no doubt that during this period the power of preventive measures, which I have already shown can definitely affect the mortality from the disease, has had its effect. The limitation of the opportunities for repeated infection, perhaps more especially by segregation, to which Dr. Newsholme has drawn attention, must be credited with some part of this improvement. The better conditions of living now prevalent must have played some part in raising the resistance of the nation. Few will, I think, deny that part of this diminished mortality is due to improved medical knowledge and improved methods of treatment. It is unquestionable that a larger proportion of

consumptives has been cured in the popular sense of the term during this period than formerly. As we are all, or nearly all, infected at some period of our lives this tends to show that we have acquired a greater resistance to the disease. In other words, a larger proportion of sufferers have acquired at any rate a partial immunity to tuberculosis. Is it impossible that these people have transmitted a partial immunity to the disease to their descendants? This view was suggested by Dr. H. Maxon King at the London Congress on the basis of observations on 242 cases of tuberculosis which occurred in his own practice. It has so far received little consideration, but it merits investigation, for if there is any truth in it, it affords suggestive evidence to account for the fall in mortality in nations where adequate preventive measures are taken, and amongst which an increasing number of people are cured of the disease, and so acquire for themselves a partial immunity.

Calmette's experiments throw a little light on this part of the question. This observer has shown that if an animal is infected with a dose of bacilli which is just sufficient to cause a lesion with which the animal is capable of dealing and from which it recovers, it is a matter of some difficulty to affect that animal with subsequent larger doses, at any rate of more difficulty than in the case of an animal which is, in the first instance, given a dose which is sufficient to produce a caseating lesion—that is to say, the first animal has acquired a partial immunity. The same thing is often seen in medical practice; for example, a child who has suffered from tuberculous glands and has got well is less likely, in our experience, than others to suffer from pulmonary tuberculosis in adult life. Man is therefore capable of acquiring a partial immunity to tuberculosis. Can he transmit this? As the immunity is partial we cannot expect much result in one generation if it is transmitted, but a succession of generations of persons with acquired immunity might lead to some transmission. In a community in which opportunities for infection are limited as much as possible, and in which adequate medical treatment is rewarded by an increasing proportion of arrested cases—that is, of cases with an acquired immunity—it would appear that the incidence of the tuberculosis diminishes. In a community in which fewer preventive measures are taken, and in which medical treatment is rewarded by fewer cases in which a partial immunity is acquired, the incidence of the disease does not show the same steady diminution, but, as in Ireland, tends to increase.

If we look at infective disease as a whole, there is some evidence to show that when such a disease has been endemic—as opposed to

epidemic—in a community for a long period of time it tends to become of a milder type. Thus syphilis is held by some to have become, in Mr. Jonathan Hutchinson's words, a much less virulent malady in Portugal from this cause. The same thing is held to be true of small-pox, measles, and scarlet fever. Conversely, there is some evidence to show that when an infective disease is introduced to a new community—a virgin soil—it is of a more severe and fatal type than when it occurs in a community which, through many generations, has been accustomed to its prevalence. An example of this is the introduction of measles to the Fiji Islands in 1875. The natives had not previously suffered from this disease, and this epidemic produced 20,000 deaths in four months. Another example is the introduction of syphilis to Greenland. So far as tuberculosis is concerned, M. Cornil has reported that the natives of Patagonia did not know pulmonary tuberculosis before the installation of the English mission. The missionary's wife suffered from consumption. She collected a number of native children round her who were better fed, clothed, and housed than their brethren. In spite of this "a veritable epidemic of acute phthisis" appeared in their midst. M. Cornil states that the history of colonization shows many other examples. One further instance is the report that of late years the incidence of tuberculosis has made enormous strides amongst the native population of South Africa, who, a few years ago, were practically free from the disease. It is suggestive in the light of the above that Dr. Shrubsall has found, and my own experience is the same, that an Englishman who contracts tuberculosis in the East, such as Singapore or a Chinese station, usually offers less resistance to the disease than the Englishman who contracts it in his own country, in spite of the fact that the consular reports seem to show that in the natives of these countries the disease is of a comparatively mild type.

My purpose has been to show that our knowledge on the subject of any hereditary influence on tuberculosis is far from complete. Certainly the evidence in favour of an inherited predisposition is not sufficiently strong to make me vary my practice of refusing to advise those who have suffered from pulmonary tuberculosis, and who have acquired a partial immunity in the process of the arrest of the disease, to refrain from marriage.

A general survey of the whole subject suggests that the following conclusions are not wholly wide of the mark :—

(1) The hereditary transmission of the germ is so infrequent that it is a negligible factor.

(2) The incidence of tuberculosis depends in the main on two factors: (*a*) exposure to infection, which in turn is governed by the dose received and the virulence of the particular strain of bacillus; (*b*) the undermining of the resistance of the individual by insanitary conditions and by disease.

(3) The more adequate the preventive measures taken in any community the less are the incidence and mortality of the disease.

(4) The more adequate the medical treatment—that is, the greater the proportion of persons in whom the disease has been arrested, and who have thereby acquired a partial immunity—the less are the incidence and mortality of the disease.

(5) As at death we all, or nearly all, show evidence of having at some time been infected with tuberculosis, and as most of us are able to overcome the infection, it is clear that the diminished opportunity for repeated infection, brought about by preventive measures and better medical treatment in this country, cannot wholly account for the diminishing incidence and mortality of the disease.

(6) There is some evidence to suggest that the diminishing incidence and mortality of the disease may be in part due to a partial immunity inherited in the course of generations from tuberculous ancestors in whom the disease has been cured.

(7) The theory that there is an inherited predisposition to tuberculosis is based on insufficient evidence.

Professor KARL PEARSON, F.R.S.: Mr. President and Gentlemen,—I feel great hesitation in speaking to-night, because I occupy a sort of third position which is hardly recognized, on the one hand, by the medical profession, nor, on the other hand, by the biologist—namely, that of the mathematician or statistician. I fancy, however, that most of the cases that we have seen on the screen and heard discussed during the last two evenings call for some slight aid from the mathematician if the results are to be logically interpreted. At the same time he is liable to make very serious blunders if he goes without the biologist on one side and the medical man on the other. The mathematician admits that at present he can only progress with the help of these crutches on either side. I have to thank Dr. Latham for courteously sending me a copy of his paper, but I am afraid I have not had time to consult medical friends with regard to several points in it.

Before I go on to discuss tuberculosis I should like to allude to one or two matters which I have heard mentioned during these two evenings.

With regard to Dr. Mercier, I sympathize very largely with what he said about the need for obtaining statistics of normals as well as of abnormals. I have endeavoured, in my own small way, to obtain such data by collecting records of normal families, and my number of pedigrees reaches about 400 now. But real inferences cannot, I think, be drawn until we have a random sample of at least 1,000 cases. The bulk of these cases has been provided by medical men—not necessarily by medical men who ask questions in hospital practice, but by medical men who know their patients and their patients' families fairly thoroughly—and that leads me to emphasize a point with regard to the collection of all such pedigrees. It is extremely difficult in a London hospital to obtain accurate results. Personally, I think the London population is decidedly inferior to what we get in the North of England or in Scotland. The memory of the peasant in the North of England and in Scotland is far greater, and the pride of family is far more intense than you get in the average Londoner of the general hospital population. I refer to that because I think that Dr. Rivers's tuberculosis statistics, based on a very sympathetic acquaintance with his patients and not filled in from a single simple inquiry, are not subject to the criticism which Dr. Latham has passed upon them.

Before I go on to refer to tuberculosis I should like to say a word about Dr. Mercier's paper. He started with a statement about mutation with which we are not all agreed, and he held that Mendelism had been proved true for at least some things. My own standpoint is that there is no definite proof of Mendelism applying to any living form at present; the proof has got to be given yet. We saw on the screen last time one or two pedigrees which were supposed to illustrate Mendelism. I saw a remarkable pedigree which is known as Weil's pedigree; it will be familiar to most of you, and quite recently Dr. Weil's son has carried that pedigree down one or two generations. Among the changes produced in it is the inheritance of diabetes insipidus, or polyuria, through a non-affected member. Such cases are rare, but that they exist seems highly probable. Again, I saw on the screen certain pedigrees of human albinism. Now, albinism is a subject which I am peculiarly interested in at the present time. I have been busy, in conjunction with Mr. Nettleship and Mr. Usher, in collecting pedigrees of albinism from all parts of the world. We have 600 or 700 pedigrees, including about 5,000 albinos. I saw three pedigrees on the board which were supposed to indicate that Mendelism applied to albinism. I take it most people would say that albinism, if anything, is a mutation,

but when you come to investigate the subject of albinism and inquire what you are to do with a given case which is represented as that of an albino, extraordinary difficulty arises as to how you are to classify it at all. No simple category, like albinotic or non-albinotic, can cover this difficulty. There may be lumps in your frequency curve, but there is every grade of albinism not only in man but also in animals. Individuals may have been all their lives through regarded as complete albinos, but when the post-mortem takes place they show pigment in more than one direction. Are they to be spoken of as albinotic or as non-albinotic? The classification into broad categories, like albinotic and non-albinotic, may be helpful in a first handling of the subject, but it is not one you can carry through when you are dealing with the question of whether ratios in large numbers follow Mendelian rules. And I believe that statement to be true for all sorts of things in which what are said to be Mendelian characters occur or do not occur. I could give you other illustrations of characters which are said to be present or absent. The difficulty in all these cases is to know whether the *degree of presence* justifies us in stating that they are present or absent. If you obtain from competent ophthalmologists and other well-trained medical men descriptions of what they term albinos, and afterwards obtain hair, or in exceptional cases portions of the iris, you will find that some people who have passed as albinos all their lives are not wholly wanting in pigment. We find almost every albinotic grade. Pigment which cannot be recognized ophthalmoscopically and can only be found microscopically very often exists. In the case of the hair of albinos, nearly 100 specimens have now been examined, and there is cellular pigment in nearly every one of them. There is a granular pigmentation in many of them. There is often less granular pigmentation in people who do not pass as albinos at all. What I want to point out is this: that division into categories, albinotic and non-albinotic, split foot and no split foot, have no very definite bearing when you come to analyse individual cases. If you take a split-foot family you may find that what is called split foot may differ from one individual to another by as many as thirty bones. I specially mention this because, in the case of many other characters besides albinism, it is an extraordinarily difficult thing to put your cases under two classes. As I say, we saw three pedigrees of albinism put upon the screen last Wednesday, due to Dr. Magnus, of Christiania. He is a remarkably careful worker, and he has undertaken in recent years a very complete investigation of albinism in Norway. He is perfectly catholic in his ideas of inheritance, and, being perfectly

catholic, he sent thirty of his pedigrees to Professor Bateson and to myself. He asked me if they fitted in with my theory, and he tells me he asked Professor Bateson how they fitted in with Mendel's. All I can say is that of those thirty pedigrees—I will not speak of the 600 we have—the principles required by Mendel fail utterly. It is no good showing two or three on the board; you have to take the whole number. I have cases at present where either a normal or an albinotic woman married two husbands, who were no relations to her nor to each other. Some offspring by both parents were albinos. All three stocks, according to Mendelian hypothesis, ought to have albinism in a recessive form. You can calculate the chances against that because an albino occurs in Italy about 1 in 30,000, in Norway in about 1 every 20,000 of the population, in Scotland 1 in 24,000. What are the chances that a woman of albinotic stock would marry two stocks affected with albinism and not related either to her or to each other? I have no fewer than four or five such cases. I have another case of a negress: she married first a Frenchman, and she had an albino child; she then married a negro, and she had an albino child. The hypothesis must be that the Frenchman and the negro, neither of whom were related to the negress, had albinism in a recessive form. That sort of improbability multiplies. I do not say there is any conclusive proof against the truth of Mendelism; I say we have not at present got the data to judge Mendelism by—the material we want needs to be multiplied a hundred-fold. I think Professor Bateson will agree with me in that. And, further, we want good material. The only way to get that is to collect facts—facts in the present case with regard to man, facts first and theories afterwards. When we have enough data, then we shall be able to draw theoretical conclusions. I do not think that at present there is any warrant for such definite opinions as we have heard to-night—namely, that there is a distinction between an ordinary variation and a mutation, or a distinction between one form of inheritance and a second. I believe the real service which has been done by Mendel and Mendel's followers lies in showing the importance of noticing segregation. The great fact of segregation holds, whether Mendelism in its simple form holds or not. There is certainly segregation in the offspring of the second generation. Mendelism has done an immense service in setting a large number of people experimenting and collecting, but I am perfectly sure it is too early in the day to assert that it holds for man—and I would go a step further: that it holds for any plants or animals.

Now, having said so much on the general point, I should like to turn, if I may, to Dr. Latham's paper.

Professor Bateson: I showed the pedigrees of albinism as an example of a character which did not follow our rules.

Professor Pearson: I am extremely glad to hear that. I am sorry that I should have mistaken Professor Bateson's meaning at the last meeting. I thought it came as one of the things which were, somehow, supposed to follow the Mendelian rules. I understand, then, that it differs in man from the rules for animals? (Professor Bateson: Yes.) You hold it to apply to animals? (Professor Bateson: Certainly, in many animals.) But by misunderstanding Professor Bateson I do not think I shall have wasted your time, because it is possible that one or two others may have also failed to quite understand that these special pedigrees were supposed not to conform to Mendelism.

Now with regard to Dr. Latham's paper, to which I have not had time to give a long study. I understand he supposes that a certain degree of immunity is acquired, and, further, that this degree of immunity, being acquired, is inherited. I did not hear him, in stating that, say that he was proposing to accept the hypothesis of the inheritance of acquired characters. But surely at the present day, if we assert that acquired characters are inherited, we must at once make a very strong statement to our audience that we differ from the weight of present biological opinion. If acquired characters are inherited, I am afraid Mendelism and every theory we have of dealing with heredity at present collapses. But it does not matter, as far as Dr. Latham's criticism of my own work goes, whether the immunity which is inherited is, as I think probable, natural or whether it is acquired. The measure of inheritance, at any rate, is there. But in the case of Dr. Latham the inheritance is attached to an hypothesis which I believe the great bulk of biologists would say was untenable—namely, the inheritance of acquired characters.

If we turn from this first point for a moment, and look at the actual problem before us—that, not of the inheritance of a disease, but of the inheritance of a diathesis or special constitution—I think it is conceivable that the weakness of the inherited constitution can lie in one particular organ. And therefore, when I came to touch the subject of tuberculosis, I carefully inquired among medical men with considerable experience whether it was desirable to club together all forms of tuberculosis or keep them separate. The prevailing opinion given to me then was that it was desirable to keep pulmonary tuberculosis apart from other forms of tubercle. But supposing we did include all forms, and supposing tuberculosis really is inherited in various types—that is to

say, that a general constitution is inherited—what would be the effect of our inclusion? We should *intensify* the apparent heredity. The leaving out of other types would merely weaken the intensity of the inheritance. In other words, to argue that they have been left out only means that we ought to have got a far higher degree of inheritance than we have, had we included them. All Dr. Latham's criticisms amount to this: that if your statistics are bad, they ought to increase the strength of inheritance; you ought to get a spurious, an artificial value from them. But, on the contrary, every time you weaken your statistics you approach more and more nearly to the condition of picking up at random two men in the street and asking them if they have got the disease, and then correlating them as father and son. The result of that would be that you would find your relationship zero. Every argument in Dr. Latham's address as to the incompleteness of our statistics and as to the fact that certain forms of tuberculosis are left out only tends to show that instead of reaching the same value for our intensity of inheritance as we have found for physical and other characters in man, we ought to have found phthisical inheritance much more than the observed size; that is to say, his arguments tend to show that we have only got a *lower* limit to the inheritance. In order to criticize our results, he must start from the statistical standpoint and show that the actual relation found on the numbers is somewhere statistically wrong. The fact that the pedigrees are poor, which I do not for a moment believe because I know much care has been exercised in their preparation, would only weaken the intensity of the inheritance and lead us to results which should show a low degree of inheritance.

Now, if I might keep you a moment longer, Sir, there is a question in my own mind whether the fact that Dr. Latham cited with regard to the reduction of disease is not really due to the survival of the fitter. It seems to me that the survival of the inherited immunity is quite sufficient to show the reduction we find in the disease. I know that will not be very popular here, for the medical man naturally likes to think that the fall is due to his efforts. I am not at all sure that it is not largely due to the prevalence of tuberculosis in the last few generations. Dr. Latham said if there were 50 per cent. when the record is completed of offspring of tuberculous parents affected, then tuberculosis ought to increase. Why? I should say if the population be stable, there would be just 50 per cent. of tuberculous people in the next generation. Fifty per cent. of the children of tall parents may be tall, but it does not follow in the least

that the whole population is getting taller. Stability, *if there be no selection*, would give you the same percentage in the next generation. I am inclined to think there is very much greater selection than Dr. Latham allows for, because I find that while the fraternities of the tuberculous are very large—averaging 6·7 and running up to 10 and even 13—the offspring of the tuberculous give you a less average number of children. In other words, however late you may be in postponing the period at which tuberculosis produces death—and, remember, the period to which you postpone death is not the same thing as the period at which you begin to find a man or a woman incapacitated and recognizing that it is not a desirable thing for him or her to have children—the "modal" period for the onset of the disease is still 25 to 28 years. I think there is absolutely nothing inconsistent with 50 per cent. of the offspring of tuberculous people being tuberculous, when the pedigree is completed—*i.e.*, when all offspring have passed alive through the danger zone. And the decline, so well marked in this chart, I look upon as the result of a pure selective process, the survival of people with an inherited immunity in various grades, and not with an acquired immunity.

I appear to be very dogmatic to-night, gentlemen, but a little dogmatism occasionally is a good thing. It stirs people up to think and inquire; and what we want at the present day is to get a wave of inquiry as to family histories started in the medical profession; we want men who will spend time and energy not in asking questions of hospital patients, whom they see once or twice, but in following up cases. It is not a light task to form a pedigree. You may need to write thirty or forty letters, or to see ten or twenty people, before you have tested it and got it completed. Every pedigree is, in itself, almost a work of art, and it has got, under those conditions, a permanent scientific value. If only one medical man in ten would once in his life construct two such pedigrees we should have, in the course of a generation, all the material needed to answer these questions of the inheritance of deformity and of the constitutional tendency to special diseases.

Dr. J. E. Squire, C.B., said he spoke with considerable diffidence after the speech which had just been delivered, because it showed what many had realized—some for a number of years—that the statistics upon which they had been, to some extent, obliged to rely were absolutely fallacious. His only justification for coming forward in the discussion was that he had some years ago brought forward statistics

on the subject of heredity in consumption, although he was obliged to confess that they possessed all the inherent defects which had been alluded to and which could only be fully appreciated by a trained statistician. When, fifteen years ago, he brought before the Royal Medical and Chirurgical Society statistics dealing with inheritance in connexion with consumption, the belief that inheritance was the all-important factor was general. The way in which, as a rule, statistics had been compiled was to ask patients who were suffering from consumption questions directed to finding out what were their own parents' histories. By that method of inquiry it was found that about 33 per cent. of the people who were suffering from tuberculosis gave a history of tuberculosis in one or both parents. But if one went the other way to work and looked to the consumptive individual, and traced his children, it would be found—as he had found—that again 33 per cent. of the children of tuberculous parents themselves developed tuberculosis. So that by both methods one arrived at a figure which might be, and was, taken as an estimate of the influence of heredity in pulmonary tuberculosis, for that was the chief object of the present inquiry. In drawing up his own figures he went to work in another way; taking the families of the tuberculous, he ascertained how many of their children afterwards developed tuberculosis; he then took the families of non-tuberculous parents, to see how many of their children developed the disease. In both cases he dealt with the same class of people, so as to be able to see what influence was exerted by environment. The figures he obtained showed that of the children of tuberculous parents, 33·15 per cent. afterwards developed tuberculosis, and of the children of non-tuberculous parents 24·6 per cent. So the influence of heredity was apparently diminished to about 9 per cent. It was true that amongst the children of families in which both parents were tuberculous the proportion of them who afterwards had the disease was as high as 43 per cent. But that 9 per cent. of difference noted above might indicate the extra risk of infection run by children brought up in the families of consumptive parents, whilst the difference between 24 per cent. and 43 per cent. might represent the extra risk of those who are exposed to a double risk of infection. The figures at least served the useful purpose of directing attention to the possibility that hereditary influence was not so important a cause as had been supposed, and that environment and occupation might be more powerful etiological factors. Tuberculosis itself, being the result of a bacterial invasion, was not in itself hereditary or inherited—it was only susceptibility which could be

considered in this connexion. He supposed everyone would now agree that human beings possessed susceptibility towards infection from tuberculosis, which differed in degree if not in quality from that possessed by animals of a different species. There was, apparently, a racial susceptibility to the tubercle bacillus common to all human beings. What they wanted to know was, Is there, in addition to and beyond that, some special specific susceptibility which the tuberculous parent handed down to his offspring? In all diseases which were common to human beings—of which measles might be taken as an example—there were certain individuals, and perhaps certain families, who were more prone to suffer from infection, both in the readiness with which they became infected when they were exposed and in the severity of the disease when they had become infected. The point was, Was the difference which was found in individuals and families due to a specially inherited property, and, if so, was that inherited property sufficiently potent to form an important etiological factor in the production of the disease? He thought not. It was known that environment in the widest sense of that term, occupation, and previous diseases influenced very largely the susceptibility of the individual to suffer from tuberculosis; and it was obvious that before one could put down in any pedigree the incidence of tuberculosis in the children of tuberculous parents it was necessary to eliminate that important factor of environment. There was also very great difficulty in obtaining the information which was needed. It was impossible that every individual of several generations could be examined by skilled men, and amongst the public the term "consumption" was a very elastic one, and was held to cover a wide range of conditions. Recently he was called upon to examine in a large school fifty children who were said to be suffering from consumption; he found in only one-sixth of that number evidences of the disease. That would show the extreme difficulty of obtaining the necessary facts from mere hearsay evidence. He granted that when those facts had been collated it required a skilled statistician to work them out and point the conclusions; possibly that functionary had some elaborate formula which enabled him to calculate the possibility of error, even in such things as the frequency with which the right name was given to a disease; or it might be done by the old-fashioned rule—to guess at a quarter and multiply by four. The point he wished to make was, that all the skill of the mathematician would help very little unless reliable facts could be obtained. It was certain that in taking only two or three generations it would be found that diseases were

called by names which they did not merit at all. Tuberculosis was a disease which seemed to affect most individuals—at least a German observer had said that an individual who had not got tuberculosis either had had it or would get it. In any case, so widespread a disease permitted such opportunities for fallacy that he feared that at the present day one could not rely on the results which had been arrived at by the statistical method. And with regard to the other method—the experimental—that had to be put out of court for the human being. He would sum up his own opinion as follows: All human beings possess a racial susceptibility to tuberculous infection which is probably transmitted from generation to generation, but there is at present no sufficient evidence that any *special* specific predisposition is transmitted from tuberculous parents to their offspring.

Dr. Bashford, in opening the discussion on cancer, said: A general discussion of the part played by heredity in causing cancer in families or individuals must at the present time be imperfect and largely hypothetical. For this reason it is that aspect of recent investigations on cancer which I should least have ventured to bring before this Society but for the fact that I have held it to be my duty to respond to the invitation of Sir William Church to lay before you the imperfect materials at my disposal and the principles on which I believe they should be interpreted.

The successful application of the comparative and experimental methods appears to be greatly narrowing the field of inquiry and dismissing many explanations of cancer—previously held with good reason—from further serious consideration. Although this is the case, we still know very little as to its etiology beyond the fact that it manifests itself under the most divergent conditions and in such a way that we may entertain the possibility of several etiological factors, some of which are external and some internal to the body. To these factors we are only justified at present in assigning an indirect or mediate etiological significance. The most satisfactory explanation of the causation of cancer will probably be that implied by the accurate description of the nature of the transformation of normal into cancerous cells, when this advance in knowledge shall have been attained.

In surveying the incidence of cancer in the vertebrate kingdom, one has been struck by the fact that certain forms of cancer appear to preponderate in different classes. It is, of course, obvious that the incidence of cancer in representatives of the different zoological classes

must differ, since, *e.g.*, structures peculiar to mammals are absent in other vertebrates. But if we consider the mammalia themselves, it appears probable that some species are very liable to forms of cancer from which others, even nearly allied, are relatively or altogether exempt, as illustrated, *e.g.*, by the variations in the frequency with which cancer of the uterus or mamma occurs. Cancer of the breast, so common in the human female, is also common in the mouse and dog, but practically unknown in the cow, which, however, suffers quite frequently from primary growths of the liver and adrenal. These tendencies are so constant that it is difficult to escape the conclusion that they depend on innate characters which are hereditarily transmissible, and there can be no doubt as to their etiological importance, although we cannot yet penetrate to their meaning.

Even in the same species we meet with similar idiosyncrasies, *e.g.*, in the greater liability of grey than of other horses to melanotic sarcoma. It may, of course, be argued that these peculiarities of incidence of the disease are determined by peculiar environment or by the use to which the organs are put in different species, although this would hardly hold for grey as contrasted with other horses, the disease in question affecting only the pigment-cells of the skin. If we compare the tame albino mouse with the wild grey mouse, the incidence of cancer is parallel in them, although the two varieties live under very divergent conditions; therefore the liability of the mouse to carcinoma of the mamma appears to be due to an innate tendency.

When we compare the large natural groups of vertebrates, or even the species of the mammalia, the grounds on which we may assume that differences in the incidence of cancer are innate and hereditarily transmitted appear safe. But when we come to compare the differences in the incidence of cancer in the individuals of a species we are not on such certain ground.

We know most about cancer in man. The extraordinary frequency of cancer of the skin of the abdomen in Kashmiris as compared with Europeans would at once suggest some racial difference were it not that we know the causative factor in this case to be one of custom. The Kashmiris wear a charcoal oven against the abdominal wall, and Europeans do not. Many other instances could be quoted, all pointing in the same direction. Taking the surface of the body as an example, the incidence of cancer in different races of mankind is characterized, on the whole, not so much by innate racial peculiarities as determined by extrinsic irritants. Why some individuals escape the consequences

of peculiar practices involving chronic irritation, and others do not, it is at present impossible to decide. Disregarding all other hypotheses, we fall back on an undefined susceptibility of the body, which we conceive as being more exaggerated in some persons than in others. There is certainly no evidence for the inheritance of cancer as such—only the possibility of a predisposition can be discussed.

To ascertain the part heredity may play in leading up to this predisposition we can resort to statistical or to experimental methods. It is quite possible to discuss the part heredity may play in the incidence of disease without discussing any other causative factor; but in any such attempt the investigator will be biased according as his standpoint is, that the particular disease under discussion is purely endogenous or purely exogenous in origin. Now, although it would be without the bounds of my subject to make an excursion into the cause or causes of cancer, I think it well to preface what I have to say regarding heredity by stating that in recent years a great deal of new evidence has been accumulated in support of the view that a malignant new growth contains nothing foreign to the organism attacked. I may instance two classes of new facts:—

(1) Carcinoma and sarcoma can be continuously grown only in other individuals of the same species of animal. The continuous growth which follows transplantation can only be prevented by vaccinating with the normal tissues or malignant new growths of the same species, and the degree of protection normal tissues confer is so much the greater, the more nearly the tumour transplanted corresponds to the normal tissue used to induce protection. From these observations it is deducible that the malignant new growths of a species retain not only the tissue characters of the species, but also the biochemical, as well as the histological characters of the several tissues of the individual species.

(2) Investigations into questions of metabolism, viz., into the relation of a malignant new growth to its host have shown (*a*) for sporadic tumours in Dr. Murray's experiments; (*b*) for Dr. Murray's and Dr. Haaland's experiments on transplanted tumours; (*c*) for Dr. Cramer's, Dr. Copeman's, and Dr. Hake's experiments on the gastric secretion in mice affected with spontaneous and transplanted cancer; and (*d*) for Dr. Cramer's observations on the gaseous metabolism in rats bearing transplanted sarcoma, that the relations of a malignant new growth to its host are merely those of nutrition—of the demand for, and the supply of, the normal foodstuffs from which tissue is built

up, analogous to those obtaining between fœtus and mother. There is no evidence of pathological products, toxins, ferments or what-not, which *per se* cause ill-health. There is no analogy with any known form of infective disease; and this being so, we may seek primarily for the cause of cancer within the body itself, in the biological properties of its cells as contrasted with exogenous causes.

The fact that cancer may develop as a response to diverse external agencies, acting as mediate causes, is thereby not excluded, although its ultimate origin is sought in a biological alteration of what were normal cells. This conception of the origin of cancer seems to indicate that a variable, and perhaps inherited, predisposition or vulnerability towards excitants is not a possibility to be lightly dismissed. How otherwise are we to explain why one patient responds not at all, another with a chronic ulcer, and a third with a malignant new growth at the site of irritation, in which series of events the nature of the irritant appears to be of less moment than the point to which it is supplied, and the points of application themselves may be anywhere on the surface of the body?

An endeavour to ascertain by statistical methods whether heredity selects those who suffer from cancer requires, at the outset, a clear conception of its distribution among the population as a whole and of the nature of the evidence which would justify us in deducing that those who suffer from it are afflicted because their ancestors also succumbed to the disease. For these purposes a combination of the methods employed by Mr. Harrison Cripps [1] and Dr. Ogle [2] can be employed. It is therefore necessary to point out how frequent cancer is as a cause of death in those members of the community generally who are above 35 years of age, and because this is so to anticipate that if heredity play any part it will be a dominant part. On the assumption that an inborn tendency to cancer is transmitted we will expect to find, if we examine a large number of families of which one or more members have suffered from cancer, that the number of cases occurring in them greatly exceeds the average number in the population as a whole, regard being, of course, paid to distribution for age and sex. On a closer analysis of the family histories of those who suffer from cancer and of those who do not, we would expect the population to

[1] W. Harrison Cripps. "The Relative Frequency with which Cancer is found in the Direct Offspring of a Cancerous or Non-cancerous Parent," *St. Bart.'s Hosp. Reports*, 1878, xiv, p. 287. *Vide* also "Cancer of the Rectum," 1880, pp. 6-13.

[2] "Fifty-second Annual Report of the Registrar-General of Births, Deaths and Marriages in England (1889)," 1890, pp. 13-14.

fall easily and naturally into two groups: (1) in which the disease develops not at all or only as a rare variation, and (2) in which it appears and reappears with constancy in a very high proportion of all the lineal descendants who attain to the "cancer ages." If this easy grouping should not be attainable, it will not be permissible to resort to subsidiary assumptions to explain why the disease appears to skip a generation or generations in the direct line of descent, or to make up for the deficiency of the evidence of lineal transmission by bolstering it up with the irrelevant occurrence of cancer in collateral descendants. To be obliged to have recourse to either the one or the other of these supports is tantamount to discarding the thesis that if hereditary, then it will be so in proportion to the degree of concentration of the hereditary factor.

The great frequency of cancer is best illustrated by the returns of the Registrar-General, which show that in 1906, out of a total of 141,241 deaths of males above 35 years of age, 12,695 were from cancer, and out of a total of 140,607 deaths of females over 35 years of age, 17,671 were from cancer. Thus the chance, assuming no more heredity than is shown by an average member of the entire population, that a man over 35 will die of cancer is 1 in 11, and the chance for a woman above the same age is 1 in 8. The following table, based on a similar approximation for 1905, shows how often, taking the proportions as 1 in 12 and 1 in 8, no death, or one, two, three, &c., deaths from cancer may be expected to be recorded in 100 families, half the members of which are men and half women, *no hereditary tendency being assumed* beyond what is indicated above, and excluding all persons dying under 35:—

Number of cancer deaths in family	Per 100 families of 6 members, viz., 3 men, 3 women	Per 100 families of 8 members, viz., 4 men, 4 women	Per 100 families of 10 members, viz., 5 men, 5 women
None	51	41	33
One	36	39	39
Two	11	16	20
Three or more ...	2	4	8
	100	100	100

The foregoing table establishes the fact that, when no hereditary influence is assumed, the frequency of cancer as a cause of death is so great that few families of large size escape; and in one of every two families either a parent or a grandparent will, on an average, have died of cancer, supposing such parents and grandparents to have died after 35 years of age. Suppose a man and wife, both of whom died of cancer sixty years ago; further suppose that, of their children, three males and

three females all survived and married, and that two of them, one male and one female, married children of parents who died of cancer like their own parents, while the others married into families with no history of cancer. Were it possible to follow the fate of all descendants of these six families, the comparative frequency of cancer in those of double cancerous heredity and in those of single cancerous heredity might be expected to show whether a tendency to the disease is transmitted. Were accurate detailed analyses obtainable of the incidence of cancer in a large number of families, and if they showed great variations in accordance with the frequency of cancer in their progenitors, above and below the average given in the preceding table, the division of the population into groups with and without a family susceptibility would be practicable, and the investigation of possible hereditary factors feasible in the case of man.

The segregation of the general population into such groups is, however, rendered very difficult because the great frequency of cancer as a cause of death in adult life discounts very largely any value which might otherwise attach to a succession of cases, or to its mere appearance and reappearance in a family, as evidence of heredity; the peculiarities of its age-incidence make it difficult to know what proportion of relatives has suffered or would have suffered had they lived long enough. It is not so easy to ascertain how many attained to "cancer age" as it is to learn how many relatives, *e.g.*, brothers and sisters, were born. It must be confessed that a segregation of families into those relatively liable to and relatively exempt from cancer has not as yet been satisfactorily attained, although attempted repeatedly. It is not difficult to collect a number of family histories of those who have suffered from cancer, but it is difficult to the point of impossibility to make these histories complete genealogical trees for three and even for two generations. What is of even more import is the difficulty[1] of bringing the data for such limited numbers of families into relation with the population generally in a way which may justify a comparison between them so as to be sure that cancer is really more frequent in some families than in others. For the determination of the importance of heredity we are

[1] The difficulty is less when the question put is that of contrasting parents with the generation sprung from them, and with certain reservations it may be overcome in this case; but it is a counsel of perfection to assert that the question put should be a comparison between the frequency of cancer in the general population and in the total number of relatives of families with a cancerous history. The one is a statement of a practicable, the other of an impracticable, inquiry. The two statements, however, really involve one and the same problem.

concerned with the comparison of the frequency of cancer in parents and children. It is immaterial whether we reason from groups of cancerous and non-cancerous children to their parents, or from cancerous and non-cancerous parents to their children. What we are seeking for is the evidence of the *hereditary transmission* of cancer, and the relation between its occurrence in parents and children will be revealed as well by the one method as by the other if the data can be obtained.

The evidence we have to rely on is, I am afraid, of a very imperfect kind and of the following nature. It may be considered under four heads corresponding to a grouping of the data obtained: (*a*) Where no history of cancer was obtainable and the family history not properly recorded; (*b*) where no history of cancer was obtainable, but the family history was recorded; (*c*) and (*d*) where a history of cancer was obtainable and the family history fully or imperfectly recorded. In the two years 1906 and 1907, reports on 2,932 patients suffering from malignant new growths, in which the clinical diagnosis had been confirmed by microscopical examination, were received by the Imperial Cancer Research Fund.

(1) Of these 2,932 cases the space assigned to records of the family history was not filled in at all or contained a record stating that the family history was doubtful as regards the occurrence of cancer in "ascendants" or "collaterals," or showed the family history had obviously been carelessly inquired into in 2,263 cases. Therefore, in three out of every four cases there was either no knowledge on the part of the patient that near relations had suffered from cancer or carelessness on the part of the recorder of the family history of the patient. It is a priori quite intelligible, as many investigators have stated, that the class from which hospital patients are drawn is ignorant of the causes of death and even of the life-history of their ascendants and collaterals, the exigencies of existence causing them to fall out of touch with the family. The fact that no reliable statement was obtainable for 2,632 cases out of a total of 2,932 must be in the main referred to these circumstances or to the circumstance that cancer as a matter of fact had not occurred in the family. The weight which will be attached to these alternatives will doubtless depend upon the bias of the inquirer. Those supplying the information to the Imperial Cancer Research Fund may be looked upon as reliable and unbiased observers, and their inability to supply information was in all probability the consequence of insurmountable difficulties in attempting to elicit positive information. Nevertheless, the large proportion of patients corresponding to 4,526 parents, and a

much higher but unknown number of collaterals in whom no evidence of cancer was obtainable, are very striking. Even allowing for the imperfections of the records, these figures are an example of the kind of evidence which is advanced to show the occurrence of few cases of cancer in a large number of relatives. There are no data which permit us to deny that the 4,526 parents of these 2,263 cancer patients actually suffered from cancer in the same proportions as the general population—viz., 1 in 11 men and 1 in 8 women. The same may be said for the collaterals. The fact that no statement was made does not justify the assumption that the incidence of cancer in the parents of these patients was less than in the general population, and we must therefore restrict our reasoning to those family histories in which definite statements as to the occurrence or absence of cancer were made.

(2) There remain 669 cases to be considered. It was definitely recorded for 358 patients, the number of whose brothers and sisters was also stated—and, judging by this fact, they were well informed of their family histories—that no other case of cancer had been known to occur in the family. These 358 cases of cancer are therefore to be regarded as sporadic cases, without heredity; 358 cases without family taint out of a total of 669 families is such a high proportion that if such records are to be relied upon a family taint evidently is not the sole foundation upon which cancer develops.

(3) and (4) Cancer was recorded in one to four blood-relatives of the remaining 311 cancer patients. Thus out of 669 patients suffering from cancer whose family histories were obtainable, cancer is recorded as having occurred in the relatives of 311—*i.e.*, in 50 per cent. But as we have already seen, the mortality from cancer is so great that, on an average, in one of two families either a parent or a grandparent will have died of cancer without assuming hereditary predisposition. Hence the use made of such records to prove the occurrence of a large number of cases of cancer in a selected number of families is not warranted.

The 311 patients with a family history of cancer had 359 cancerous relatives. The father was attacked fifty-eight times and the mother 114 times, or 1 in 5·4 for fathers and 1 in 2·7 for mothers. This appears to be a very much higher rate than occurs in the general population for males and females above 35 years of age. A crude calculation of this kind appears to be the usual method by which the figures for family histories of cancer are utilized to bring out evidence of heredity. In it no account is taken of the families of the 358 cancer patients for whom complete histories were obtained, showing no occurrence of cancer in

relatives. If it is, however, not justifiable to exclude them, since doing so appears to beg the whole question, then the fifty-eight cancerous fathers and the 114 cancerous mothers occurred among the 669 male and 669 female parents of cancerous children, or 1 in 11·5 of the fathers and 1 in 6 of the mothers suffered from cancer. These proportions are as near those obtaining for the general population dying from all causes as can be expected from crude data.

No detailed reference has been made to the numbers of additional cases of cancer recorded in the brothers and sisters of cancer patients, the reason being the very good one that no approximate estimate of their respective ages at death, and no comparison with the general population is possible. It gives us no information whatsoever to find that fifteen deaths occurred in 607 brothers born, and twenty-seven deaths in 596 sisters born, and we are no further if we take the brothers and sisters only of those patients who died over 50 years of age. However, Weinberg[1] has been able to make an approximate calculation for cancer patients in the population of Stuttgart. In order to obtain a basis for comparison, he ascertained how many deaths from cancer had occurred in the family of the deceased, and also how many deaths from cancer had occurred in the families of their husbands and wives. According to data thus obtained there died of cancer, of 100 relatives :—

	Of the deceased	Of their husbands and wives
Parents	6·6 per cent. ...	5·9 per cent.
Brothers and sisters ...	3·9 ,, ...	3·1 ,,

And he concludes that heredity does not play a dominant part.

We have still to consider the importance attaching to those rare family histories with an exceptionally high incidence of cancer, or where, as pointed out by Mr. Butlin[2] in a most valuable and impartial paper, the disease appears only on one side of the family, as if introduced by some grandparent or parent; *e.g.*, such family histories as the following, kindly supplied to me by Dr. Edward Jessop, are certainly very suggestive, but unfortunately the information as to ascendants and collaterals gives out just where it would prove of value: A man, one of a family of nine, died of cancer of the liver, the others being all alive and well. The patient's mother was one of a family of

[1] Weinberg and Gaspar. "Die bösartigen Neubildungen in Stuttgart von 1873 bis 1902, *Zeitschr. f. Krebsforschung*, 1904, Bd. ii, pp. 195-260.

[2] Henry T. Butlin. "Reports of the Collective Investigation Committee of the British Medical Association," No. 13: Cancer (of the breast only).

thirteen, seven of whom (four males and three females) died of cancer. Two died of cancer of the bladder, two cancer of the liver, and one each of cancer of the throat, uterus, and breast. The patient's father died of diabetes, but his sister (the patient's paternal aunt) died of cancer of the bowel. Again, five members (four males and one female) of a family of nine children died of cancer. The four males died of abdominal growths and the female of cancer of the uterus. The mother and mother's brother also died of cancer; the father died of phthisis. The son of the eighth son died at the age of 28 of cancer of the bowel.

Family histories of this kind are, however, rare, in proportion to the number of individuals attacked, and they are mainly of interest as showing that if cancer be transmissible by heredity, then transmission takes place both through the male and the female, without anything corresponding to what is known for hæmophilia and colour-blindness. These histories are so infrequent that they cause no surprise when the table of the relative frequency of cancer in the general population given above is considered; for did these forms of family history imply hereditary transmission, then we should be able with ease to obtain tables of a hundred families in which the figures for no deaths, one, two, three, or more were the inverse of what they are in the population; but this is not the case. The isolated instances recorded in the literature serve only to show how rare this phenomenon really is. When recorded, it is more than probably to be looked upon as what would be expected to happen in the case of so frequent a cause of death as cancer, from a consideration of the distribution theoretically calculated according to the law of probabilities.

To sum up the inferences which may be drawn from the crude statistical data in man, there is nothing which one would be justified in submitting to the biometrician for nearer analysis. There is, in short, no evidence of cancer arising as a transmissible variation. It seems, then, that cancer is probably always acquired.

Turning to the experimental investigation of cancer in animals, alleged epidemics have often been recorded in them, especially for mice and rats housed together in small cages. Satisfactory proof that these aggregations of cases were due to infection has not been furnished, and the alternative explanation, that they arise as the result of in-breeding cancerous stock, has naturally suggested itself. Our very detailed observations on tens of thousands of mice have not revealed in our laboratory anything which we would call an epidemic. When, however, we

take into consideration the manner in which cases of carcinoma mammæ have been sent to us by breeders we find the same kind of evidence as that which has led observers in France,[1] America,[2] and Germany[3] to assert that epidemics of cancer occur in breeding establishments. We may illustrate this kind of evidence by the numbers of tumour-mice sent in by four of the breeders who supply us with mice, under a guarantee that no fresh stock has been introduced. From January 1, 1906, to October 31, 1907, Mr. A. sent us ten cases, Mr. B., six cases, Mr. C., thirty-five cases, Mr. D., eighteen cases of carcinoma of the mamma. These figures, which are more remarkable than any others yet published, are no evidence that there was an endemic or epidemic occurrence of cancer in the breeding-cages of Mr. C. or Mr. D. The proportions of mice supplied to us in the same period to cases of cancer were as follows:—

	Mice with tumour	Total mice
Mr. A.	10	1,302
Mr. B.	6	1,547
Mr. C.	35	9,698
Mr. D.	18	11,842

The numbers of tumours occurring in these stocks of mice have been determined solely by the number of mice of "cancer age" under observation. This is brought out particularly clearly in the difference between the age constitution of the stock of Mr. C. and Mr. D., since the stock of the latter contains constantly a much higher proportion of young animals, and he supplies us with most of our young mice. Further, if we note the dates on which tumours are sent to us and arrange them in columns, we find that the crops of tumours coincide with the ageing of groups of mice. Thus those apparent aggregations of cases, wrongly called epidemics by too enthusiastic advocates of a parasitic origin for cancer, also give no indication of haphazard in-breeding leading to a preponderance of cases of cancer of the mamma. The incidence of the disease for mice continues to obey the laws of age- and sex-distribution, even where in-breeding is proceeding haphazard.

We have therefore devoted great attention to systematic breeding experiments, of which the starting-point has been not merely mice of so-called cancerous stock, but mice which had also actually *suffered* from

[1] A. Borrell. "Epithélioses infectieuses et epithéliomas," *Ann. de l'Inst. Pasteur*, 1903.

[2] Gaylord, H. G. "Evidences that Infected Cages are the Source of Spontaneous Cancer developing among Small-caged Animals," *Brit. Med. Journ.*, 1906, ii, p. 1555. (Gives references to other literature.)

[3] Michaelis, L. "Ueber den Krebs der Mäuse," *Zeitschr. f. Krebsforschung*, 1906, Bd. iv, Heft 1, p. 1.

cancer. Thus the objection has been met of those who might argue that unless the disease had been present in the parent there was no opportunity for its transmission. The question of heredity of cancer of the mamma or of a predisposition to it is now in a fair way to final settlement. The mouse has the great advantage of having a short life, and many successive generations can be accurately observed, and age, dates of birth and death, parentage, cause of death, post-mortem examination, fully recorded. In addition, a comparison with an average sample of the mouse population is possible.

The surgical removal of spontaneously occurring mammary tumours, of which the clinical course and the pathological examination leave no doubt whatsoever that the tumours were malignant epithelial new growths, has enabled us to prolong the life of many mice and to breed from them. Breeding from such elderly mice is not an easy matter, and much patience has been necessary. By successively crossing other spontaneously affected animals with the offspring of cancerous parents, strains are being obtained in which the cancerous heredity is $\frac{1}{2}$, $\frac{3}{4}$, or $\frac{15}{16}$, and even higher. The concentration of a hypothetical hereditary factor in a *known* amount and in large numbers of animals of *known* age should in the course of a few more years definitely settle whether there is a family or only an individual liability to the disease. As yet we have obtained only a few cases of carcinoma of the mamma and no cases in other organs. Thus far there is no evidence that the liability to carcinoma has been enhanced by systematic in-breeding. I do not wish to anticipate the results of our observations, which are still continuing, but we have not as yet obtained even an indication that cancer is inherited. It appears to be very doubtful whether there is transmitted even a power of acquiring the cancerous modification under excitation, and it is not impossible that cancer may be really a late modification of healthy tissue acquired *de novo* for each individual, and in which the bogy of inherited predisposition—the dying echo of ancient constitutional conceptions of cancer as a blood-disease—plays no part whatsoever.

The question will be asked: If experiment does not as yet support the conception of an inherited predisposition, why does cancer arise in one individual and not in another who has been subject to the same irritant on the same region of the body? One of the most important results of experiment has been the absolute demonstration of the truth of the belief, to which, I suppose, we all subscribe nowadays, that cancer is primarily circumscribed. The fact that occasionally there may be more than one primary focus in the same individual or that a single focus may comprise a number of centres does not fundamentally affect this

view. Another important result of experiment has been the demonstration that the conditions of origin are fundamentally distinct from the conditions of mere growth into a tumour, and a third, the proof that the soil provided by a mouse or a rat can be experimentally modified in two directions. It can be rendered absolutely unsuitable or more than normally suitable for the growth of transplantable carcinomata and sarcomata. It has been amply shown that the tame mice of England differ in their susceptibility to transplantation from those of France, Germany, or Denmark. Haaland has shown that the descendants of German mice may be modified by prolonged sojourn in Norway. Other investigators, especially Gierke, have observed a similar change in English mice after prolonged sojourn in Germany. Another form of constitutional influence which is of moment, at any rate in the case of some transplantable tumours, is that the presence of a primary tumour can effect a secondary modification favourable to dissemination and metastasis formation. Observations have also been recorded, but are as yet unconfirmed, that the histological structure of a tumour can be modified by the influence of the "soil."

There are therefore constitutional conditions which are favourable and others which are unfavourable to the growth of cancer, and they can be induced experimentally at will. An analogous relationship may subsist between the subject of spontaneous cancer and the tumour—*e.g.*, in man. Then the consequences of the circumscribed primary cancerous change would depend upon the condition of the "soil" in which it is taking place, from causes either within or without the body.

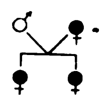
In conclusion, with nothing but negative evidence of the part played by inherited constitutional conditions before us, and with positive evidence of the important part acquired constitutional conditions can play in furthering the growth, and perhaps the development of cancer, we shall more profitably spend our time if we frankly seek to ascertain how they are acquired than if we continue to preach the doctrine that they are inherited and that it is hopeless to contend against them.

Mr. BUTLIN[1]: Before speaking on the question of the heredity of cancer, I would say that I agree with the suggestion that, if anything is inherited, it is a "susceptibility" to cancer, which, to my mind, means that if certain other conditions are present, an individual who is "susceptible" is much more likely to suffer from cancer than another individual who is not susceptible. Of the nature of susceptibility, we

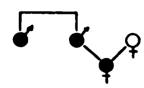
[1] Mr. Butlin reopened the discussion on November 26.

have already learned from the Imperial Cancer Research that some mice are very susceptible to the implantation of cancer, while other mice of the same race, under similar conditions, exhibit a refractoriness to implantation which may amount to immunity. And we infer that what is true for mice is probably true for men. Again, from the same source, we learn that some mice are almost certainly born susceptible, while other mice of the same breed, and under precisely similar conditions, seem to be born immune to cancer. And, again, we infer that what is true for mice is probably also true for men.

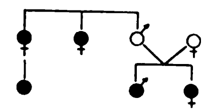
We then have only to consider whether the susceptibility which some individuals possess from birth is inherited. The opponents of the theory of heredity seem to me to take too narrow a view of the influence of heredity. They object to the use of cases in which the inherited condition skips a generation, and to other cases in which inheritance is claimed on the ground that members of collateral branches have suffered from cancer. They scarcely seem to me to take into account how far-reaching the influence of inheritance is on the one hand, or how it may seem, on the other hand, to be so limited that it appears to be subject to caprice. Take, for example, such cases as the following. (Cases were given to show the skipping of generations and the inheritance of common qualities by members of collateral branches.) A further example may be found in connexion with the condition which we call hay-fever, which is generally believed to be largely due to inheritance. It is not truly a disease, for it consists solely in an extreme sensibility of some areas of the mucous membrane to the presence of the pollen of hay. Last week a gentleman who was consulting me for quite another trouble mentioned incidentally that he suffered from hay-fever. I inquired of his family history. He told me he was one of eleven children and that only he and one brother were subject to hay-fever. He did not know whether the trouble existed in previous generations, but did not think it did. His brother died comparatively young. He himself is married and has five children, of whom one only, a boy, 10 or 12 years old, suffers from hay-fever. If we accept the inheritance of the sensibility in the case of this boy, as most of us would be disposed to do, we have to admit that the same sensibility was not inherited by the other four children, for the proof of the presence or absence of this sensibility is easy to determine. Again, a boy is admitted into the hospital with a single exostosis, and there is no family history of a similar condition. Many such boys may be admitted into the Metropolitan hospitals in the



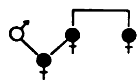
Three cases; mother and sister.



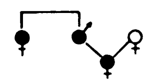
One case; father and father's brother.



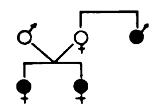
One case; brother, two of father's sisters, and father's sister's child.



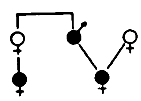
Three cases; mother and mother's sister.



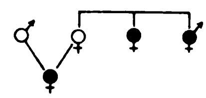
One case; father and father's sister.



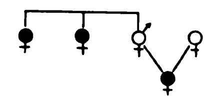
One case; sister and mother's brother.



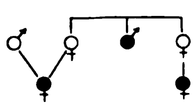
Two cases; father and father's sister's daughter.



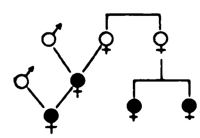
One case; mother's brother and sister.



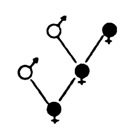
One case; father's two sisters.



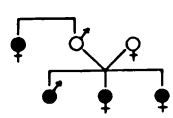
One case; mother's brother and mother's sister's daughter.



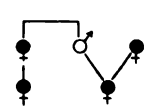
One case; mother and two of mother's cousins.



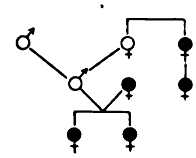
Two cases; mother and mother's mother.



One case; brother and sister and father's sister.



One case; mother, father's sister, and daughter of father's sister.



One case; sister, mother, father's mother's sister and her daughter.

FAMILY HISTORIES OF PATIENTS WITH CANCER OF THE BREAST, TO SHOW HOW THE CANCEROUS RELATIVES ARE GENERALLY ON THE FATHER'S OR THE MOTHER'S SIDE, NOT SCATTERED AT RANDOM.

course of years, and there may be no family history of exostosis in any case, from which it might be inferred that this condition is never inherited until, one day, a boy is admitted with multiple exostoses, and tells that his father suffers from a similar condition. Examination of the father and the son proves that this is so, and the resemblance may be so striking that no figures or statistics or arguments would suffice to destroy the conviction of the observer that the boy inherits the tendency to the growth of exostoses from the father.

Some of the foregoing instances are almost trivial; it is on that account I have related them, for our belief in the influence of heredity depends quite as much on the frequent occurrence of trivial conditions as on the occasional occurrence of the most striking resemblances. As a matter of fact, we admit that the shape of the nose, the colour of the eyes and hair, qualities of the mind (such as courage and cowardice, meanness and generosity), and strength and weakness may be inherited. We admit that weakness of certain organs and tissues of the body may be inherited, or an extreme and unique sensibility of a particular surface or part of a surface may be inherited. We admit that abnormalities may be handed down by inheritance, and I suppose we may still be permitted to believe that a tendency to gout may be inherited. But when we come to consider the possibility of the inheritance of a susceptibility to the occurrence of a particular disease we are met with the objection that we are not in a position to prove it by statistics.

We have, however, furnished some kind of proof of the justice of our view in the history of certain families in which cancer is singularly prevalent, and other evidence to which I shall presently refer. I quite admit that this evidence is very imperfect; but I hold that the force of logic is on our side and that the burden of proof lies with those who deny the possibility of an inherited susceptibility to cancer. So far as I am aware, there is no evidence on that side. And the only arguments with which I am acquainted are those which were put forward with singular skill thirty years ago by my colleague, Mr. Cripps, in an article in our *Hospital Reports*,[1] and which were repeated last week by Dr. Bashford. They may be summed up thus: exclude those families in which the disease has skipped a generation, and those families in which the theory of inheritance depends largely on cancer in collateral members, and those families in which the disease is not of the same

[1] *St. Bart's. Hosp. Reports*, 1878, xiv, p. 287.

variety in all the cancerous members; and there is then no evidence left by which to establish the theory of heredity. For there are a certain number of cases of cancer in this country every year, and it cannot be expected that these cases should be exactly evenly distributed. Therefore, if one large family has no case of cancer, another large family must provide at least two cases. Naturally, we decline to accept these restrictions, which are quite unwarranted. It is further objected to our evidence that our susceptible families do not exhibit a sufficient number of cases of cancer and that no regular proportion is observed.

I would reply to this objection by the statement of a case. A man consults me on account of a cancer on the border of his tongue. He attributes it to an injury by a rough and carious tooth. There is leucoplakia and superficial glossitis on the affected border of his tongue. He is 50 years of age and has a clear history of syphilis and of much tobacco. Looking at the etiology of the disease, I assume that the injury was the exciting cause, that the predisposing causes are his age and the condition of the border of his tongue, and that the condition of the border of his tongue would probably not have been present had it not been for tobacco and specific disease. Finally, I must find a place for susceptibility. But it stands a long way down on the list. This man may have four brothers, each one equally susceptible to cancer as himself. But not one of them suffers from cancer, because the other causes are absent. Such a case illustrates well the small part which susceptibility may play in the occurrence of cancer. On the other hand, it is a cause of such importance that, if it had not been present in this person, all the other conditions not merely might, but perhaps must, have failed to induce the occurrence of the disease.

I had no intention, Sir, of taking part in this debate, for my attention has been so much occupied with other problems connected with cancer that I have neglected the problem of heredity. But when I found my name in Dr. Bashford's paper I looked out the work to which he referred and determined to defend it. It is contained in a report which I wrote twenty-one years ago for the Collective Investigation Committee of the British Medical Association.[1] The report was founded on returns to certain questions which had been furnished by the Committee to medical men in various parts of the country. At that time I was, I am sure, to some extent under the influence of Mr. Cripps's clever paper, for I began to analyse the returns with little

[1] *Brit. Med. Journ.*, 1887, i, p. 436.

expectation that they would furnish any valuable evidence in favour of the theory of inheritance. But by the time I had completed my work I was forced to admit that they had furnished evidence of a kind which, so far as I am aware, had never previously been observed. All the cases in which more than one relative of the cancerous patient was affected are comprised in these charts, and, with two exceptions, they all show the same thing, that the cases of cancer in the previous generations, instead of being scattered irregularly on the mother's or the father's side, were all on one side or the other. In one of the two exceptions, the father's sister and her daughter were affected as well as the mother of the patient; in the other, the father's aunt and her daughter as well as the mother and sister of the patient. I am quite ready to admit that these charts are very imperfect, for they do not give any account of the other members of the patient's family or of the number of persons in each generation of the family. But such and so imperfect as they are, they may fairly be accepted as one more piece of evidence in favour of the theory of heredity. It must be remembered that they were derived from many separate sources, and were not collected for the purpose of showing what they do show. Nor did I select certain examples out of the returns, but have here furnished the charts of *all* the families in which there was more than one cancerous relative of the patient.

Sir John McFadyean: I regret to say that I am not able to contribute anything useful to this discussion in so far as that relates to the influence of heredity on diseases of the nervous system or cancer. Those diseases of the former class which are of special interest in this connexion can scarcely be said to occur among the lower animals, or, at any rate, they occur so rarely that they afford no material of value for estimating the role of heredity in the etiology of nervous diseases. One may almost say the same of cancer. All the principal varieties of neoplasms, benign and malignant, are met with among the domesticated mammals, but there is no statistical material that is of any real value in the present connexion. It is true that there is one rather remarkable kind of tumour—the so-called melanoma of the horse—in the causation of which heredity undoubtedly plays an important part, since the disease is rare in horses of any other colour, and greyness in horses is, I believe, entirely determined by heredity. But the tendency to the disease is obviously co-related to the pigmentation of the hair in these animals, and there is no evidence that it is stronger in any particular breed or

family of grey horses than in others. The case is, therefore, of such a special kind that it warrants no inference as to the probability of inherited tendency to other varieties of neoplasm in the other domesticated animals or in man.

It is otherwise in the case of tuberculosis of animals, and especially of bovine tuberculosis, as the material there is abundant, and an examination of the facts does throw some light on the question of heredity. The belief that calves were frequently born tuberculous was at one time very generally held both by breeders and veterinary surgeons. It may safely be asserted that this was not a conclusion arrived at independently, but simply the extension to bovine tuberculosis of the opinion widely held regarding human consumption. That the opinion was erroneous was first proved by observations made in large Continental slaughter-houses, which showed that the proportion of young calves showing lesions of tuberculosis was less than 1 per cent., even in places where the adult cattle were found on slaughter to be affected in the proportion of 20 per cent. All subsequent investigations have confirmed the conclusions which these observations justified—viz., that, with exceptions which are negligible from a practical point of view, calves come into the world free from tuberculosis. It is true that some people have declined to admit that the rarity of visible lesions in new-born calves proves that infection prior to birth is rare, maintaining that at birth, and for some time afterwards, the disease or the bacilli are present, but inactive or latent. This is an absolutely unfounded assumption, and it is definitely disproved by the fact (1) that, with rare exceptions, new-born calves do not react to tuberculin, and (2) that when new-born and non-reacting calves born of tuberculous parents are reared in circumstances that shield them from infection they remain free from the disease.

When it became impossible any longer to maintain that the so-called congenital tuberculosis played any part in the spread of bovine tuberculosis, the view was revived that a special predisposition to the disease was transmitted, and that such transmission was the important factor in determining the incidence of tuberculosis among different breeds and races of cattle. At first sight this view appears to be, at least, plausible. It has long been held that tuberculosis is much more prevalent in some breeds of cattle than in others. In this country, for example, Shorthorn and Jersey herds have always been supposed to furnish an exceptionally large proportion of tuberculosis as compared with the other breeds of cattle. Similarly, in Scotland tuberculosis is thought to be specially frequent among animals of the Ayrshire breed.

It is probably a fact that these breeds do furnish an exceptional proportion of victims as compared with all the other breeds of cattle in this country taken together, but the incidence of the disease in different breeds is not so widely different as many people have supposed. This fact, however, in no way justifies the contention that the predisposition to tuberculosis varies in the slightest degree in the different breeds of British, or, indeed, of European, cattle. The argument to the contrary involves a very obvious fallacy. It is the fallacy which is involved in every attempt to measure the resistance to tuberculosis by comparing the incidence of the disease among different groups of individuals without allowing any weight to the fact (1) that the disease is contagious; (2) that the opportunities for infection may have been widely different in the groups compared. When these facts are kept in mind and are accorded the importance to which they are obviously entitled, the alleged evidence in favour of a special predisposition of certain breeds of European cattle absolutely disappears. Every variation in the incidence of the disease can be simply and naturally explained by dissimilarity of environment, which must involve unequal risks of infection. This can, perhaps, be presented most clearly when one remembers that to ascribe a high incidence of the disease in certain groups or breeds of cattle to a special predisposition is equivalent to affirming that the normal condition of cattle is to be immune against the disease, or, at least, to possess such a degree of natural resistance that they can withstand all ordinary risks of infection. Now it is obviously as absurd to affirm that certain breeds of cattle are naturally immune against tuberculosis because they are exempt from it as it would be to pronounce the individuals of a regiment that had never been in battle bullet-proof because none of them had ever been wounded.

If time permitted I could adduce many observations pointing to the conclusion that, at least in this country, all breeds and strains of cattle are susceptible to tuberculosis, and that when the environment is the same the incidence of the disease is the same in all breeds and strains. The proportion of cases of tuberculosis furnished by any breed is high or low according as the conditions in which the animals are bred and reared provide more or less opportunity for the transference of tubercle bacilli from the diseased to the healthy. Jersey cattle are free from the disease in their native island, not because they are immune, but because the disease has not yet been introduced into the island. Whenever they are brought to this country and placed in infected herds they furnish just as large a proportion of cases as any other breed. Highland cattle and

other mountain breeds are either free from the disease or are rarely affected as long as they remain at large on their native pastures, but they readily contract the disease when housed with tuberculous cattle. The Chartley herd of British wild cattle was nearly exterminated by tuberculosis, which was probably introduced by domesticated cattle that were allowed to come in contact with them during recent years.

The question whether it is natural immunity that preserves entire species of animals from tuberculosis is of little interest when the point being discussed is whether varying predisposition, received by inheritance, is an important factor in the spread of tuberculosis among human beings, but it is of interest because of the emphasis which the ascertained facts give to what has already been said regarding the fallacy involved in taking incidence of disease as a measure of susceptibility without paying any regard to the influence of environment in favouring or hindering infection. Until lately sheep and goats were popularly supposed to be immune against tuberculosis. This is quite a mistake, for animals of both species are readily infected experimentally, and in favourable circumstances they probably contract the disease just as readily as cattle or human beings.

I have left to the last the question with regard to bovine tuberculosis which is of most interest—viz., whether there is any evidence to show that among cattle there is anything corresponding with the family predisposition supposed to exist in the human species. The answer must be in the negative. A loose notion to the contrary may be found among breeders and veterinary surgeons, but no instance supported by respectable evidence has ever been put forward. Whenever the circumstances are investigated it turns out that the facts do not compel one to admit that there has been any special predisposition, since the all-important factor of opportunity of infection could not be accurately measured. But this is not the whole of the case against the view that some families of cattle are specially predisposed to tuberculosis, or, to put the same contention otherwise, that there are some families which are immune or highly resistant. There has been accumulated during the last few years a considerable body of experimental evidence which is of far more value than any observations made in natural circumstances for enabling one to measure the natural powers of resistance to infection possessed by different individuals of the bovine species. I refer to the experiments recently carried out in this and other countries in which cattle have been infected with measured quantities of tubercle bacilli. I believe I am justified in saying that these experiments have not detected

a single animal possessing powers of resistance much above or below the average for animals of the same age and weight.

The evidence with regard to the susceptibility of cattle to tuberculosis may be summed up by saying that there are absolutely no facts which compel one to admit that the incidence of the disease among bovines is in any appreciable degree determined by varying degrees of resistance or of susceptibility on the part of different breeds or families.

I venture to express the view that there is also no evidence tending to prove that there is anything deserving the name of family predisposition to tuberculosis in human beings. In almost every instance the statistics which have been cited as such evidence are devoid of value because they involve the transparent fallacy previously referred to. For that reason it appears to me to be not good advice to exhort the medical profession to record the pedigrees of tuberculous individuals, or to provide the statistical information necessary to establish the comparative incidence of tuberculosis in the descendants of tuberculous and non-tuberculous parents. Labour of this kind must be of the nature of misdirected industry, because when the figures come to be weighed no one can disentangle the effects of the hypothetical factor—inherited predisposition—from the influence of varying risks of infection and other important factors which must be admitted to be always in operation. This is not a case in which either the biologist or the statistician can lend us any assistance. At least one previous speaker in this debate has pointed out the possible fallacy involved in comparing the frequency of disease among members of the same family with the average frequency in the whole population when the cause of the disease in question is not known, but surely the risk of error is very much greater when, as in the case of tuberculosis, the disease is known to be contagious. When that fact is recognized one sees immediately what is the kind of evidence that would be necessary to prove that there is such a thing as inherited predisposition. It would have to enable us to compare the incidence of tuberculosis among the children of tuberculous parents with its incidence among equal numbers of children of non-tuberculous parents, both being subject from birth to the same environment. Even then the comparison would be slightly unfair to the children of tuberculous parents, because they must have had nine months longer of exposure to infection where the mother was diseased. Needless to say, no statistics of this kind, embracing such numbers as would justify any conclusion, have ever been obtained, or ever will be obtained, in the case of human beings.

Dr. Latham has already referred to Riffel's statistics bearing on the inheritance of predisposition, and has quoted the adverse criticism passed upon them by Cornet. But even if these statistics had been accurate and had embraced much larger numbers, it is obvious that they would not have justified any confident conclusion as to the part played by inheritance of predisposition in determining the incidence of tuberculosis. To compare the death-rate from tuberculosis among the progeny of healthy parents with the death-rate from the same disease among the progeny of tuberculous parents is fallacious unless the individuals of the first category have been born in infected houses or placed there immediately after birth. The children of tuberculous parents are in nearly all cases exposed to quite special risks of infection, (1) because, being born in an infected medium, they are more liable than the children of healthy parents to be infected while still young; and (2) because the dose of infective material introduced into their bodies is likely to be exceptionally large, even if one assumes that tubercle bacilli are so widely diffused that no one in civilized countries can expect to escape them altogether. And these two factors are probably of very great importance, not only in determining infection, but also in determining the course of the disease after infection. It seems impossible to deny that the resistance to infection and to the progress of the disease after infection is less in children and in young animals generally than in adults, and this fact alone would account for a wide difference in the incidence of the disease among the children of tuberculous and of non-tuberculous parents. But the dose or quantity of the bacilli which cause the primary infection is probably of still greater importance as a factor determining the course of the disease after infection. At any rate, that appears to be established by the results observed in the last few years in the experimental infection of young cattle. These experiments have disclosed a fact which at first sight appears to be very puzzling. It is that, whereas the naturally contracted disease in cattle is usually of a type so mild and benign that only a small minority of infected individuals ever show any outward symptoms, the disease set up in young animals by inoculation, even with what are reckoned small doses of bacilli, is almost invariably of a virulent type, and determines death within two or three months. The explanation of this remarkable difference appears to be that experimental inoculation is usually effected with doses which, although reckoned small, are really enormous as compared with the number of bacilli which in any natural circumstances are ever simultaneously introduced into the tissues of a healthy subject. In

natural primary infection as a rule only a small number of tubercle bacilli are taken in or are admitted into the tissues, and the natural defences of the body are able to hold these in check, while time is thus allowed for the development of greatly increased powers of resistance. That many naturally infected animals possess exceptional powers of resistance as compared with healthy subjects is easily proved by experiment. On the other hand, in experimental inoculation, in which relatively large numbers of bacilli are simultaneously introduced into the tissues, the natural defences of the body are, so to speak, "rushed," and the bacilli are able to gain the upper hand before the system has had time to develop increased powers of resistance.

These considerations enable one to understand the extent to which the children born of infected parents, and plunged immediately into an infected medium, are handicapped, and they appear amply sufficient to account for family infection without calling in the agency of either inherited disease or inherited predisposition.

Dr. GOSSAGE said he wished particularly to bring forward the point that in human beings it was found that there were certain definite characters or abnormalities which were handed down to descendants practically without alteration or mitigation, and without diminution in the number of the affected. Conjoined with that was another circumstance, namely, that when the abnormal person married—so few were the abnormals in these rare conditions—he usually crossed with a normal, and when that happened the result was that some of the children were normal and some abnormal. They were not a mixture with characters between the normal and the abnormal. The progeny of the normal were normal. In order to explain those facts one necessarily required a theory, and the only theory which offered any explanation was that of Mendel. Facts respecting human beings were not susceptible of confirmation by experiment, and without such confirmation the facts were not sufficient on which to found a theory. But Mendel's theory did not depend on facts gathered from human beings, but from plants and the lower animals, where the facts had been subjected to rigid experimental investigations in the laboratory. It was also found that the numbers of human progeny did approach very closely to what would be expected on Mendel's hypothesis. When a normal person crossed with an abnormal, one would expect half the progeny to be normal and half to be abnormal, and it nearly came out at that. It was necessary to consider the question of the condition being handed

down more or less unchanged. It was true that abnormal individuals were found to vary considerably, just as normals did. But on the whole the children were found to be as severely affected as their parents, being sometimes more affected, sometimes less. The question of albinos was raised at the last meeting, when it was said that there was no really sharp line of distinction between the albinos—that is, the abnormals—and the normal in regard to the presence of pigment. Dr. Garrod would be able to say more about that subject. But even supposing there was no sharp line, there was very little difficulty as a rule in placing the individual in his proper category, whether he was abnormal or normal, even where there was some overlapping. Usually in the conditions referred to there was no overlapping. It had been said that the number of the affected tended to become less as time went on. It was the rule to find in these families that there was a diminution of the number of abnormals in succeeding generations. That was susceptible of a very obvious explanation—namely, that the abnormal individuals in the past were remembered, whereas the normals were not remembered. To be quite accurate it was necessary that the normals as well as the abnormals should be recorded in every generation. Another point was that the abnormality being passed down from an abnormal individual, one found in the previous generations that only the progenitor was mentioned and no members of his family. But if only the last two generations were taken, as being the most accurately recorded, it would be found that there was no decrease in the number of abnormals in the last as compared with those in the generation before. He incidentally took out the numbers with regard to certain families, the particulars of which he had collected. Among nineteen families of those exhibiting the condition known as tylosis palmaris et plantaris, in the last generation there were sixty-five affected and fifty-seven unaffected; while in the last generation but one, eighty-four were affected and seventy-nine unaffected. About another condition, epidermolysis bullosa, he had obtained data from thirteen families, and in the last generation sixty-four were affected, fifty-six unaffected; and in the generation before, fifty affected, seventy-six unaffected. It was easy, too, to find in families a small increase in the unaffected in the last generation—for instance, in families of diabetes insipidus—but taking all conditions together there was neither increase nor decrease of the abnormal offspring of abnormal parents compared with the normal with the progress of time. There was, it was true, a tendency to the increase of the normals in the total descendants of an individual, because his normal offspring, marrying with other normals, would beget only normals.

Another objection which had been raised to the application of Mendel's law to human beings was that there were exceptions—*i.e.*, there were instances where the abnormality was handed down through a normal individual. Inheritance in the case of animals was often fairly complicated, and there was no reason for supposing that human heredity was any less complex. There were quite a number of conditions which seemed to have been handed down at times through normal people. The instance of diabetes insipidus quoted last time was the first in Weil's great family, but instances of the same thing occurred in Gee's family, as he (Dr. Gossage) had pointed out last April. The same phenomenon had also been recorded in the case of epidermolysis bullosa. The number of normal individuals capable of handing down the abnormality was strictly limited. One could not say how limited because the exact method of the laboratory could not be applied; there were a considerable number of normal individuals who had not been bred from, and until they had children there was no means of knowing whether they were capable of handing down the abnormality or not. A number of circumstances might occur to account for the passing of an abnormality through a normal person. For instance, for a particular character to show itself in offspring it might be necessary for there to be two factors present at the same time, each of which might be derived from one parent. That was found to be so sometimes in plants and animals. Here it could be predicted what the progeny would be, on Mendel's law, and experimental breeding had verified the prediction. Again, in plants and animals it had been found that there might be a deterrent factor present, which would prevent the character showing itself. The character, too, might be present in the parent and yet not show itself. This had been shown in the case of fowls with extra toes by Professor Bateson. It was justifiable to say that what occurred in animals could occur in human beings, although in the lack of experiment we were unable to unravel the exact method of human inheritance.

With regard to sex-limited abnormalities, some conditions, such as colour-blindness, were distinctly sex-limited; the male was the only one affected, except when a male was crossed with a female who also carried the factor for colour-blindness; *i.e.*, the female might have the factor present, but did not manifest it. Where a male carrying the factor for colour-blindness crossed with a female who carried it, it was possible to have a female who was pure with regard to colour-blindness, and then that female would be colour-blind. All the male children of such a colour-blind female were found to be colour-blind, as expected theoretically.

Another more or less sex-limited disease which should be mentioned in such a debate was hæmophilia, which was said by Grandidier to be *par excellence* the inherited disease. As a rule, it affected only males and was transmitted mainly through females. The reason for the latter was fairly obvious—namely, that the majority of the male subjects did not live sufficiently long to be able to beget children. Some males were affected with it less severely and were able to arrive at adult life, and when they bred they passed the condition on to some of their children, and some of their children were able in turn to pass it on. It was not, however, strictly sex-limited, because some of the females who could transmit the disease showed it. In them the symptoms did not, as a rule, begin to show themselves until the subjects were approaching maturity. A considerable number of females said to have that condition did not really show it; the evidence was based on occasional severe epistaxis or profuse menstruation. He confessed that the numbers in hæmophilia were not what would be expected according to Mendel's law; the hæmophiliac male was found to have too few of his male children affected with the condition, while the female capable of transmitting it had too many of her male children affected—nearly double the expected number. What the explanation of that was he did not know; it was a matter which the future must ascertain. Hæmophilia, however, was handed down unaltered to the descendants without diminution in intensity or numbers. Affected males handed it down to some of their male children; some of their female children could transmit to some of their male progeny, and through some of their female descendants. Unaffected males and *some* of the females could not transmit it. Mendelism offered the only explanation of these phenomena, although there were many details which could not yet be understood.

Dr. SHRUBSALL: Unfortunately, hospital records rarely yield much direct information bearing on the problems of heredity, partly because of the small number of items in the *questionnaire* bearing on this topic, but still more because of the lack of information shown by patients as to their family history. The notes usually give details as to the existence of tuberculosis in the family and to any contact between the patient and other tuberculous individuals, whether by sharing a room in common or otherwise. The cases have been classified so as to distinguish between those whose parents suffered from tuberculosis and those whose parents were with reasonable certainty believed not to have so suffered, and those concerning whom information was lacking or doubtful. The latter

class are entirely excluded in the present analysis. Two groups, then, are available—those presenting a direct hereditary taint and those without. These have been further subdivided according to the presence or absence of evidence of contact with tuberculosis. The following were determined for each class: Age of onset of tuberculosis; type of onset and of disease; type of onset in relation to age and environment; result of treatment in hospital; and the total duration of illness in fatal cases.

Age of Onset.—The age at which the symptoms of disease appeared was ascertained by deducting the duration of symptoms from the age on admission.

TABLE SHOWING THE AGE OF ONSET OF PULMONARY TUBERCULOSIS.

	Cases with no history of heredity	Total cases with a direct heredity	Direct heredity but *no* history of contact	Direct heredity *and* a history of contact	History of contact but *not* of heredity	Total cases with a history of contact	No history of either contact or heredity
MALE:							
Average age of onset (A)	29·45	26·82	34·39	22·17	24·73	22·92	30·42
Probable error ± ...	0·20	0·34	0·53	0·29	0·33	0·22	0·15
Standard deviation (σ)	10·05	10·22	9·98	6·66	6·34	6·76	10·00
$\frac{\sigma^2}{N}$	0·12	0·26	0·64	0·19	0·24	0·11	0·15
Number (N)	850	395	155	240	168	408	682
FEMALE:							
Average age of onset (A)	25·45	25·65	28·07	22.65	21·60	22·10	26·43
Probable error ± ...	0·30	0·30	0·39	0·42	0·57	0·33	0·32
Standard deviation (σ)	9·47	8·85	7·93	8·71	8·38	8·29	9·75
$\frac{\sigma^2}{N}$	0·18	0·21	0·34	0·40	0·73	0·24	0·23
Number (N)	503	378	187	191	95	286	408

When the difference between two averages is greater than three times the square root of the sum of the squares of the standard deviations of the two groups averaged, divided by the number in each such group, *i.e.*,

$$A_1 - A_2 > 3\sqrt{\frac{\sigma_1^2}{N_1} + \frac{\sigma_2^2}{N_2}},$$

then this difference is too great to be explained by mere chance selection, but must be due to some definite cause acting on the members of one or the other group.

Thus comparing males with no history of heredity with males presenting a direct history of heredity, the difference between the averages $A_1 - A_2$ is $29{\cdot}45 - 26{\cdot}82 = 2{\cdot}63$.

$$\sqrt{\frac{\sigma_1^2}{N_1} + \frac{\sigma_2^2}{N_2}} = \sqrt{0{\cdot}12 + 0{\cdot}26} = \sqrt{0{\cdot}38} = 0{\cdot}62$$

and three times this equals 1·86, which is less than 2·63, so that the odds are more than 1,000 to 1 against the hereditary cases being a random sample of those without a family history of tuberculosis. This difference is therefore said to be significant.

Contrasting the same groups of female cases: $A_2 - A_1$ (A_2 being the greater) is $25{\cdot}65 - 25{\cdot}45 = 0{\cdot}20$.

$$\sqrt{\frac{\sigma_1^2}{N_1} + \frac{\sigma_2^2}{N_2}} = \sqrt{0{\cdot}18 + 0{\cdot}21} = \sqrt{0{\cdot}39} = 0{\cdot}62$$

This is greater than 0·20, so that there is no need to consider three times the value, or 1·86. The two groups, therefore, might well be random samples from the same material.

It may be noticed that the average age of onset is significantly earlier in male cases presenting a tuberculous family history, while no difference appears between the two female groups. When the history of contact is considered the indications are a little clearer, cases with a family history of tubercle but none of contact presenting a significantly later age of onset. In this group the parents had in many cases become affected with tuberculosis after the children were of an age to leave home, so that they had not been exposed to special risk of infection in early life. The age of onset in this group is just significantly greater than that of those presenting no history of either heredity or contact, from which, possibly, it might be argued that heredity had bestowed on them not a predisposition to the disease but a certain degree of immunity. The age of onset among those presenting a history of both heredity and contact is significantly earlier. In the majority of cases making up this group the patients had lived at home, often for years, during their parents' illness, thus being greatly exposed to the risk of infection. The earlier age of onset in women than men in the cases without a tuberculous family history might receive an explanation from their domestic occupations being more liable to bring them into contact with invalids under conditions favouring infection.

Type of Onset.—Since it seemed possible that the existence of a tuberculous family history might be associated with some special peculiarity in the mode of onset, this feature was determined both in the hereditary and the non-hereditary cases. Eight modes of onset were distinguished as follows:—

An *insidious* onset is one in which the patient's attention is but gradually attracted to his health; hence the dates assigned are usually somewhat vague. There has been some malaise, loss of appetite and strength, often before cough was noticed. Patients of this type may date their symptoms from a severe cold or from some illness not specially associated with the respiratory tract.

The *bronchitic* onset comprises cases suffering from typical chronic bronchitis, usually associated with emphysema, on which the symptoms of tuberculosis, such as progressive emaciation, hæmoptysis, &c., were gradually engrafted. The signs of tuberculosis were often entirely masked by the concurrent or antecedent affection, and the diagnosis was made by discovery of tubercle bacilli in the sputum. This mode of onset corresponds to a distinct type of the disease—the bronchitic.

The *pleuritic* onset comprises cases in which, after a longer or shorter interval, clinical symptoms of pulmonary tuberculosis followed one or repeated attacks of definite pleurisy, with or without effusion.

The term *hæmoptoic* onset has been strictly confined to those cases in which moderate or severe hæmoptysis was stated to be the first symptom attracting attention. The more severe the cross-examination of the patients the smaller becomes the number of cases falling in this category.

Under the *febrile* mode of onset have been included three classes: Cases beginning with a definitely acute cold, chill, bronchitis, &c., of sudden onset, the patients being previously in their usual health (these are termed the acute cases); cases beginning with or directly after an apparently typical pneumonia; and cases beginning with or directly after an attack resembling influenza and with the history of being so diagnosed by a physician.

Finally, all cases where the disease began (usually insidiously) after some previous tuberculous affection, such as caseous cervical glands, bone or joint disease, have been classed separately as cases of pulmonary tuberculosis arising after other tuberculous manifestations.

TABLE SHOWING THE FREQUENCY OF SPECIAL MODES OF ONSET OF PULMONARY TUBERCULOSIS IN RELATION TO HEREDITY.

Type of onset	All cases		Parent or parents tuberculous		Brother or sister (or both) tuberculous		No family history of tuberculosis	
	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.
MALES:								
Insidious ...	640	51·7	135	53·7	68	51·1	437	51·3
Bronchitic ...	90	7·2	28	11·1	5	3·7	57	6·7
Pleuritic ...	178	14·4	27	10·7	27	20·3	124	14·6
Hæmoptoic ...	184	14·9	38	15·1	17	12·7	129	15·1
Acute febrile ...	16	1·3	4	1·6	—	—	12	1·4
Pneumonic ...	29	2·3	6	2·4	1	0·7	22	2·6
Influenzal ...	72	5·8	5	1·9	12	9·0	55	6·4
Total febrile ...	117	9·4	15	5·9	13	9·7	89	10·4
After other tuberculous manifestations	28	2·2	9	3·5	3	2·1	16	1·9
Total ...	1,237		252		133		852	
FEMALES:								
Insidious ...	477	64·3	142	66·0	69	61·1	266	64·2
Bronchitic ...	27	3·6	7	3·2	8	7·1	12	2·9
Pleuritic ...	103	13·8	26	12·1	13	11·5	64	15·5
Hæmoptoic ...	45	6·0	18	8·4	8	7·1	19	4·6
Acute febrile ...	19	2·5	4	1·8	4	3·5	11	2·7
Pneumonic ...	22	3·0	5	2·3	1	0·8	16	3·9
Influenzal ...	37	5·0	9	4·2	9	8·0	19	4·6
Total febrile ...	78	10·5	18	8·3	14	12·3	46	11·2
After other tuberculous manifestations	12	1·6	4	1·8	1	0·8	7	1·7
Total ...	742		215		113		414	

TABLE SHOWING THE PERCENTAGE NUMBER OF THE CASES OF EACH MODE OF ONSET IN WHICH THE PARENTS WERE TUBERCULOUS.

Mode of Onset	Males	Females
Insidious	20·2	29·8
Bronchitic	29·5	25·9
Pleuritic	14·1	25·2
Hæmoptoic	20·0	40·0
Acute febrile	21·1	21·0
Pneumonic	20·7	22·7
Influenzal	6·0	24·3
Total febrile	14·0	23·2
After previous tuberculous manifestations	30·0	33·3
Total	19·3	29·0

The chief features of interest are the excess of hæmoptoic, insidious, and febrile modes of onset in female patients with a family history of tubercle. For the first of these no clear explanation presents itself, and as the actual number of cases is small no special significance can be attached to it save as an indication of early active disease. The excess

of the latter is probably due to a mixed infection brought on through living for considerable periods under indoor conditions. On the whole, heredity appears to be associated with no special preliminary symptoms.

Age of Onset in Relation to Type of Onset.—The following table shows the average age of onset for each type of onset of pulmonary tuberculosis:—

Mode of Onset	Age of Onset: Males	Age of Onset: Females
Insidious	28·9	25·6
Bronchitic	31·3	25·9
Pleuritic	27·7	25·1
Hæmoptoic	28·1	24·4
Febrile	28·9	24·1
After other tuberculous manifestations	21·8	23·0
Total number of cases	1249	725

The most significant peculiarity of the average age of onset in the different types is the earlier date at which pulmonary disease appears in those who have previously shown evidences of tubercle elsewhere.

Relation of Occupation to Type of Onset.—The relation of occupation to the mode of onset of the illness is indicated in the following table of percentages:—

Mode of Onset	Males: Outdoor	Males: Mixed	Males: Indoor	Females: Indoor
Insidious	54·3	51·7	49·9	64·3
Bronchitic	6·4	9·0	7·5	3·6
Pleuritic	16·6	13·5	13·9	13·8
Hæmoptoic	13·7	15·7	14·9	6·0
Influenzal	4·9	4·5	7·3	5·0
Acute	2·0	1·1	1·0	2·5
Pneumonic	1·3	1·1	2·5	3·0
Total febrile	8·2	6·7	10·8	10·5
After other tuberculous manifestations	0·8	3·4	2·9	1·6

This indicates that the only modes of onset characteristic of an outdoor occupation are the pleuritic and the insidious. Bronchitis is relatively most marked in those of a mixed occupation, who are exposed to sudden climatic changes. Indoor occupations are associated with the febrile mode of onset, no doubt from some mixed infection, as the excess is due chiefly to the numbers in the influenzal section. That indoor occupations should present a larger number of cases in which pulmonary disease followed other tuberculous manifestations was to be expected from the fact that under this heading are many children and others who have been unable to go out to work owing to the crippling nature of previous bone or joint disease.

Relation of Heredity to the Total Duration of Fatal Cases.—To ascertain whether heredity was associated with any difference in the duration of illness, the post-mortem records for the last thirty years were analysed. The results shown in the following table indicate no difference between the two groups, the hereditary class being a fair sample of the other. The value of χ^2 is about 5·9, both for males and females. The duration was reckoned from the date of the first symptom mentioned in the notes to that of death.

TABLE SHOWING THE TOTAL DURATION OF SYMPTOMS IN FATAL CASES.

Duration	Males				Females			
	No evidence or no history of family tuberculosis		Direct heredity		No evidence or no history of family tuberculosis		Direct heredity	
	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.
Under 1 year ...	524	39·9	51	35·0	444	42·0	48	43·1
1 to 2 years ...	418	31·8	48	34·3	335	31·6	35	31·5
2 ,, 3 ,, ...	151	11·5	18	12·9	129	12·2	14	12·6
3 ,, 4 ,, ...	85	6·5	10	7·1	62	5·9	8	7·2
4 ,, 5 ,, ...	54	4·1	6	4·3	36	3·4	2	1·8
5 ,, 6 ,, ...	22	1·7	1	0·7	13	1·7	2	1·8
6 ,, 7 ,, ...	17	1·3	2	1·4	10	0·9	1	0·9
7 ,, 8 ,, ...	12	0·9	1	0·7	9	0·8	—	—
8 ,, 9 ,, ...	1	0·1	1	0·7	2	0·2	—	—
9 ,,10 ,, ...	9	0·7	—	—	5	0·5	1	0·9
10 years and over	19	1·4	2	1·4	8	0·7	—	—
Total ...	1,312		140		1,058		111	
Average duration in years ...	2·38		2·36		2·25		2·08	

The average age of death presented no significant differences.

	No history of parental tuberculosis	Direct heredity
Male ...	31·5	29·2
Female ...	27·8	27·4

Results of Treatment in Hospital.—The results of treatment for a short period in hospital showed that a larger percentage of patients, both of whose parents had been or were tuberculous, did badly than was presented by those with no family history of tubercle, while those with one parent only affected did rather better than those with no history of heredity.

TABLE SHOWING THE RESULT OF TREATMENT IN RELATION TO HEREDITY.

Heredity	Males +	Males −	Females +	Females −
Father tuberculous	75·5	24·5	56·7	43·3
Mother tuberculous	75·0	25·0	62·1	37·9
Both parents tuberculous	59·4	40·6	53·8	46·2
All cases with any family history of tuberculosis	69·8	30·2	59·4	40·6
No family history of tuberculosis	66·5	33·5	63·8	36·2

A positive result means definite improvement. A negative result means no material improvement, downward progress, or death.

Influence of Environment on Result of Treatment and on the Age of Onset.—The effect of hospital treatment and the average age of onset were also ascertained in relation to the general conditions of environment under which the patients had lived, which were classified as follows: Urban, where the patient had been born and had always lived in a city or large town; semi-rural, where the patient had been born in the country but had migrated into a city or large town; and rural, where the patient had been born and had always lived in the country.

TABLE SHOWING THE RESULT OF HOSPITAL TREATMENT IN RELATION TO ENVIRONMENT.

Environment	Male				Female			
	+		−		+		−	
	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.
Urban	370	67·3	180	32·7	232	68·0	109	32·0
Semi-rural	111	70·2	47	29·8	58	66·7	29	33·3
Rural	127	70·2	54	29·8	54	58·7	38	41·3

TABLE SHOWING THE RELATION OF ENVIRONMENT TO THE AGE OF ONSET.

	Males Age	Males $\frac{\sigma^2}{N}$	Females Age	Females $\frac{\sigma^2}{N}$
Urban	28·9 ± 0·3	0·28	25·5 ± 0·3	0·23
Semi-rural	30·0 ± 0·6	0·93	27·0 ± 0·6	1·20
Rural	27·7 ± 0·5	0·62	24·9 ± 0·5	0·69

With the numbers at present available these results are inconclusive.

Physical Traits in Relation to Pulmonary Tuberculosis.—Finally, the attempt was made to determine whether any particular type appeared more frequently among patients suffering from pulmonary tuberculosis than among the general populace by noting the colour of the hair and eyes.

TABLE SHOWING THE PERCENTAGE-DISTRIBUTION OF HAIR- AND EYE-COLOUR.

	Hair					Eyes		
	Red	Fair	Light brown	Dark brown	Black	Light	Neutral	Dark
General population (Beddoe) ...	4·4	12·1	41·6	37·4	4·4	52·5	14·5	33·0
Patients with pulmonary tuberculosis	3·1	10·3	31·8	44·8	9·9	36·2	11·0	52·7

These results, based on two groups, each comprising approximately 6,000 individuals, show that a distinct excess of the brunette traits prevails among the sufferers from tuberculosis. The average age of onset of the disease was determined for each of these colour-groups, with the result that an earlier onset was found for the fair type, the difference being apparently somewhat greater than would be accounted for by the process of darkening which accompanies increasing age. The numbers in the table from which the age of onset was determined are less than the above owing to the additional amount of information required, single necessary facts being omitted from many of the case notes, while a large part of the foregoing data was collected in the out-patient department.

TABLE SHOWING THE AVERAGE AGE OF ONSET FOR EACH HAIR-COLOUR GROUP.

Colour	Males				Females			
	Age	Standard deviation	No.	Per cent.	Age	Standard deviation	No.	Per cent.
Red	27·8 ± 0·9	7·62	28	2·8	21·5 ± 0·9	7·26	25	3·8
Fair	26·4 ± 0·8	9·67	65	6·5	20·5 ± 0·6	6·27	46	6·9
Light brown	26·5 ± 0·3	9·48	390	39·3	24·6 ± 0·4	8·49	235	35·5
Dark brown ...	28·8 ± 0·2	9·07	402	40·4	26·7 ± 0·3	8·33	283	42·8
Black ...	32·0 ± 0·6	10·63	109	10·9	27·5 ± 0·5	6·94	72	10·9

CONCLUSIONS.

(1) That the average age of onset is slightly earlier among men in cases where there is a family history of tuberculosis. In women there is no such difference. This earlier onset may be explained by exposure to infection in early life. When contact cases are excluded the onset is later among those with a history of parental tuberculosis.

(2) That the existence of parental tuberculosis is associated with no special type of onset of the disease in the offspring.

(3) That the course and duration of the disease appear to be the same whether there is or is not a family history of tuberculosis. Home infection seems to lead to an increase in the number of febrile cases.

(4) That the results of hospital treatment are worse among those patients both of whose parents were tuberculous.

(5) That the age of onset of tuberculosis is independent of the general environment, but is lowered by all factors, such as occupation and overcrowding, which tend to encourage infection.

(6) That patients suffering from tuberculosis present an excess of brunette traits, but that the disease appears earlier among the blondes.

Mr. J. Howell Evans: It is not without temerity that I enter this field of discussion on the effects of morbid influences upon antenatal life, more particularly during the ovular or sperminal stage. In the ovum, or in the ovum and sperm, there lies the subtle and complex machinery of the tendency to reproduce its like; its like, but with variations, which variations constitute individuality. This process we term heredity, or rather, in reference to our discussion, *normal heredity*, and we wonder how much it may be affected by health or disease while the ovum and sperm are lying in the bodies of the parents of the as yet "unconceived infant." Definite data are as yet scant. Little is really known, but theories are numerous and the literature of heredity is vast.

We have already had before us many tables of statistics and descents the mathematical value of which has been called in question, but we have been told little concerning the deep mysteries of this deeply mysterious subject. Our discussion lies with the existence or non-existence of internal causes of disease, namely: (*a*) Hereditary transmission of disease, or (*b*) hereditary transmission of the basis for such disease which constitute *morbid heredity*. Inasmuch, therefore, as normal heredity must needs have been in existence prior to morbid heredity, it is obvious that we have under discussion the hereditary transmission of acquired characters derived from external causes. These external causes of antenatal pathology are, in all probability, the same as the more familiar external causes of postnatal pathology, but acting under different conditions.

The assumption of a family, sex, or race peculiarity, far from affording a final explanation, leads us to the question, How has the special peculiarity originated? The law of survival of the fittest, so strongly supported by biologists and not existing in the same unmodified form in man, upholds the inheritance of adaptation, and in relation to morbid

heredity, I would say, upholds the inheritance of acquired pathological conditions which are primarily dependent upon external causes. It seems paradoxical that an acquired pathological condition should lead to a predisposition to disease by selection in the survival of the fittest. No! The normal heredity of health is, surely, in constant conflict with this morbid heredity; transmitted diseases and anomalies are rather evidence of the breaking of the laws of heredity than of its persistence. I fear we too frequently forget the hereditary tendency to health when contemplating the stigmata of the abnormal.

Many lesions present themselves to me, not as an acquired defect, but as a primary omission in the line of evolution, not a loss, not acquired by morbidity, but never evolved—a hitherto inexplicable flaw in evolution. The comparative anatomy of the placenta tells us that placental permeability must vary in different species according to the thickness of the tissues intervening between the maternal and fœtal blood. I would like to ask the authorities on normal animal heredity who honour us by their presence, "What difference lies in the heredity of rodents and ruminants where a marked difference in the placental thickness exists?"

Antenatal life may be divided into three periods of unequal length: (*a*) Fœtal, thirty-two to thirty-four weeks; (*b*) embryonic, five to seven weeks; (*c*) germinal, indefinite, if we accept the theory of germ-plasm extending back into the lives of parents and early ancestors where in the sexual glands the ova and spermatozoa have been previously quiescent, but capable of being impressed by biochemical changes. Given the same morbid causes the difference in the pathology of these different periods depends upon a difference in the physiology; such dissimilarities are startling, and during these periods lead us to suspect that special causes, with which we are not familiar in postnatal life, have been at work. So that the pathology of the fœtus, the pathology of the embryo, and the pathology of the germ is characterized by different results which have been produced by the same morbid agents acting at different ages and amid different surroundings. The physiology of the embryo is particularly the formation of organs—organogenesis or building-up of tissues and organs, whereas fœtal life is characterized by a growing functional activity of the various organs. Embryonic pathology means abnormal formation, or even, if the disturbances are great, non-formation. Malformations are interesting and mysterious; there is no wonder, therefore, that around these anomalies produced in the embryonic period much on the question of heredity has centred. The germinal factor is, however, supported by the occurrence of several

instances of malformation in the same family, and by the experimental production of such in the frog's egg by polyspermy. Experimental teratogenesis has shown that malformations and monstrosities may be produced by acting on embryos with the same toxic or microbic agents which produce disease in the adult, the child, or the fœtus. Let us realize that human embryology is simply a series of scanty facts linked together by a series of assumptions ; we need to supplement our information by facts borrowed from the embryology of the chick and rabbit.

When the "external causes" which exert a determining influence are solved, and when the laws of even antenatal hygiene are defined and as definitely observed, when the advance of biology into the realms of embryonic and germinal life is complete, and when our mathematical

FIG 1.

Grandmother. Mother. Child.

calculations will have been accepted as approximately accurate, there will yet remain the impossibility of knowledge of the human germinal period, except by inference. As man may be the only animal affected by certain diseases, so he will still occupy the unique position of being capable of acquiring certain conditions.

An anatomical question which has engaged my attention for many years is the relation which unusual sutures and emissary channels of the skull probably bear to cerebral states which can only be observed after birth. By the accompanying lantern illustrations you will fully appreciate the far-reaching results of an injury to the communicating channels between certain intra- and extra-cranial vessels. It must be borne in

mind that the neonatal moulding of the skull is one of the severest traumatisms ~~to which we have~~ all been subjected. With the natural persistence of these anatomical variations many successive generations may evidence conditions which are invariably regarded of hereditary transference (of cerebral origin); further, may not many of these and allied cerebral conditions be dependent upon transmitted anatomical variations? One speaker has referred to the condition of spina bifida as hereditary; this, of itself, forms an extensive field for discussion. I will, at present, content myself by remarking that it is very interesting to be able occasionally to trace the cause of such in the child to a definite affection of the mother; further, the finding of the specific organism of

Fig. 2.

Helical fistula.

epidemic cerebro-spinal meningitis in the fluid obtained by lumbar puncture from the infant at birth as well as in the cerebro-spinal fluid abstracted, at the same time, from the mother, is evidence that more subtle causes of external origin are probably the predominating factors in the production of many conditions which are in the present state of our knowledge deemed of hereditary origin (fig. 1).

The ear, owing to the multiplicity of the elements surrounding the superior branchial depression which by their fusion lead to the complex conformity of the pinna, is worthy of consideration in connexion with many anomalies which are by several authorities held to be hereditary. The condition of *coloboma auris congenita* (divided lobule) may occur in

several members of the same family, as is represented by the accompanying illustrations. This anomaly in the human subject appears to be due to an absence of or delay in coalition during an evolutionary stage, and is recognized as the usual condition in some animals.

Helical fistulæ and accessory auricles are common in some families, as is evidenced by the accompanying table and by the photograph of mother and daughter (fig. 2). The next photographs are those of two brothers, one the possessor of a helical fistula, the other of a lateral cervical (or branchial) fistula; in both instances retention cysts occurred. Further occurrences in this family of allied conditions, as cholesteoma and dermoid cyst, are of interest as occurring only in the male members. The lateral cervical region abounds in such congenital

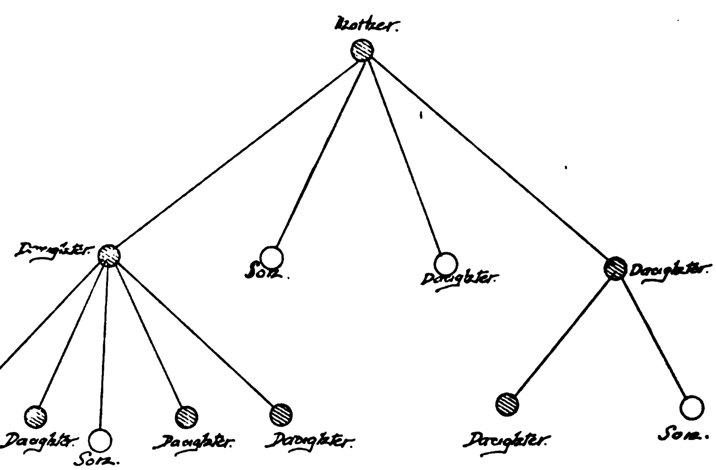


FIG. 3.
Auricular anomaly.

lesions as nævi, pigmented moles, hairy patches, branchial cysts, cervical auricles, and verrucæ (fig. 4). Cervical auricles are normal appendages in the Australian pig and certain goats, whereas verrucæ, if extensive, resemble closely the wattles of birds. All abnormalities of development have much interest when their appearance is marked by some regularity, in evidence of a common causative factor; further, as an anomaly in a certain species may be perfectly normal in another species we are led to attribute its occurrence to an evolutionary factor. Sequestrations, moles, dermoids, &c., macroscopically evident or microscopically revealed are often family characteristics—legacies of mark transmitted from parents to children.

The relation of heredity to cancer has by many been based on an assumed relation of sequestrations to cancer. Baumgarten's theory of the latency of the germ has been discarded in relation to tuberculosis—it is extremely unlikely that cancer enters the fœtus and lies sequestered in some corner to spring into evidence, perhaps, fifty years later. If these congenital lesions, *e.g.*, cysts and moles, are prone by heredity to cancer, then cancer should be expected more frequently, whereas a progressively younger age of attack should be the evidence of its telling tale. I cannot bring myself to consider such conditions as prone to cancer by

Fig. 4.

Branchial fistula (retention cyst). Helical fistula (retention cyst).

virtue of an inherent hereditary habit of growth (Adami) of their epithelial cells. The heterogeny of their cellular components and the heteromitosis of nuclear partitions afford potentialities for speculation, it is true; but, if malignancy lies in habit of growth, such would have, I venture to think, been forced upon us long years ago. These cysts, moles, and warts do not become cancer, but, like all other parts of the body, cancer may come into them. Any relation between heredity and cancer resolves itself, in my humble opinion, into the relation between

heredity and longevity, because the longer a person lives the more likely is he to get hold of cancer—or rather for cancer to get hold of him. In certain parts of the Near East there is a very high cancer incidence, but the inhabitants present a very high average age. If there is anything in cancer areas and cancer houses it directs us to environment and seed, as in tuberculosis, rather than to soil.

How many genealogical trees can show a freedom from the untimely death of a promising scion from tuberculosis? What family, whose evidence of health has been pronounced in its longevity, has been

FIG. 5.
a, Cervical auricle.

exempt from the incidence of cancer? I doubt whether there is anything which can be handed down from parent to child by virtue of the parent having cancer; if so, it is against very long odds and a very long way back. If cancer is hereditary we might expect to find it in the ovum, especially as *Deciduoma malignum* is imputed to disturbances at this early period. To enter here into a discussion upon whether all ovarian cysts are malignant and are due to a parthenogenesis would take

too long. It is, nevertheless, correct that the earliest stage of *Deciduoma malignum* may occur from the date of the blastocyte. Be it, however, remembered that the embryo is dead, and probably killed by the same external cause whose advent brings about the deciduoma.

In tuberculosis, when the seed is growing strongly upon the soil, it is at such a period of sexual activity that whatever is good or bad of the soil can have its influence upon the infant as yet unborn, but cancer generally attacks the parent at a time of life past the active sexual period ; certainly during the decline of sexual activity. This reduces the chances in both sexes, but even a further reduction follows by the relatively early cessation of the procreative sexual life of the female and by the frequency of carcinoma uteri, which, if present during the "conceptional period," tends to the expulsion of the ovum. Thus, in the case of cancer, the morbid heredity can hardly be got from the cancer itself. If it exists, we must seek elsewhere.

From certain sources we learn of a species of immunity in the relation of the blood of animals ; if so, by cancer the heredity to cancer in the offspring is diminished. *Κακοῦ κόρακος κακόν ᾠόν* embraces the popular idea of morbid heredity (Ballantyne). The bad crow may lay a bad egg, but the occasional bad egg laid by a good crow seems forgotten ; surely this occurrence is produced by an external cause.

The germ-plasm tends to normal organs performing normal functions and a constant tendency to correct errors, so that the most hereditary of all things in the world is the normal heredity of health, which is occasionally broken in upon by external causes producing morbid heredity. Suicide is not the answer to the riddle of inherited pathology. Castration is not the solution of degeneracy, but a clean mode of life to return to health as favoured by the germ-plasm. Though I cannot see in our present state of knowledge any evidence of heredity in cancer, I must acknowledge that I have dealt neither with the heteromorphoses of diseases nor with the influence of an intermediary—such may be, firstly, another animal ; secondly, a state of body induced by another condition which may be hereditary ; or, thirdly, the fœtus itself (by its marconigrams of telegony). It is obvious that, under the circumstances, it would be unwise to attempt to formulate a principle *re* cancer on the data at our command.

If heredity shall, hereafter, be shown to exert an all-pervading influence in cancer, I maintain it is an unseasonable view to predominate our present researches until further ground has been cleared by the many zealous workers in this domain.

Dr. Heron: More than thirty-five years ago I was a member of the resident medical staff of one of the largest county lunatic asylums in this country. The asylum stood not far from the county town, and at the times set apart for the purpose a considerable number of the relatives of the patients visited them in the asylum. Many of these relatives were the children, fathers, mothers, brothers, and sisters of patients. A common subject of conversation among the members of the resident medical staff was the low level of intelligence so common among these relatives, for we had numerous opportunities of seeing and conversing with them. One of their most striking characteristics was stupidity—their evident difficulty in understanding simple words used in their ordinary sense in telling of common things. Marked slowness of apprehension expresses, perhaps well enough, what I wish to convey to you touching this low level of intelligence. From this low-grade stock had come many inmates of the asylum, and they illustrated various types of insanity—from the acutely maniacal and the profoundly melancholic to that most pitiful of human beings, the gibbering, drivelling idiot. Such observations as these, concerning the insane and their nearest blood-relations, are so often recorded by medical men who have had asylum experience that I believe we are justified by their evidence in coming to the conclusions that most of the types of insanity seen in lunatic asylums spring from a stock characterized by low-grade brain development, and that the factor of heredity does tell and in no small measure on the incidence of insanity. It is, however, beyond doubt that many cases of insanity, besides those of general paralysis, cannot be traced to a low-grade stock. Whether the low-grade brain is a survival of the unfit or a throwing back to an old-time low-grade ancestry I do not know. Certain it is that this low-grade type is not uncommon, and variants of it are often found in everyday life. These variants become most noticeable in times of unusual popular excitement—for example, during religious revivals, or while a keenly contested general election is to the fore. At such times we are, I think, prone to detect low-grade brain development among people whose political and theological opinions are strongly opposed to our own.

When we know the cause of cancer we may then be able to speak with authority on the rôle of heredity in that disease. If, however, we guess at the cause of cancer, I think most of us would say that the disease will be found to attack us chiefly, if not altogether, through the alimentary tract, and to be due to an infection. Should that guess turn out to be a fact, it would seem reasonable to say that the arguments which best apply

to heredity in its connexion with infective diseases, and especially with tuberculosis, apply with equal force to the problem of heredity as it affects the spread of cancer.

There is no doubt that tuberculosis is a striking example of the power of heredity to ensure perpetuation of a disease. Cholera, typhoid, scarlet and relapsing fevers, measles, diphtheria, ague, rabies, all illustrate the fact that heredity has a great part in the tragedy of disease and death. All these diseases result from infection of the healthy by the diseased individual. This is also true of tuberculosis, and the evidence of that truth is as strong concerning tuberculosis as it is about any disease known to us. Everyone knows we are prone to the diseases just mentioned, and to many others besides, because we are born with a peculiarity of body which makes us markedly apt to catch certain infections. The proneness to fall victims to these infections is an ancient characteristic of all men. In this sense, but, I submit, in no other sense, does heredity govern the incidence of tuberculosis among men and beasts. Before 1882, when Robert Koch demonstrated the truth about the cause of tuberculosis, practically every authority on medicine in this country, and in most countries, believed the disease to be mainly dependent for its existence upon a peculiar hereditary tendency in certain families, in consequence of which they fell easy victims to tuberculosis. Even during 1882, when we first knew that tuberculosis could result only from infection, doubts began to be expressed as to the soundness of the widely accepted theory that a peculiar hereditary taint was the great factor in the incidence of that disease.

A year or so later one began to hear it said that hereditary tendency to tuberculosis meant that the bodies of certain people furnished a soil peculiarly suited to foster the growth of the tubercle bacillus. Some twenty years ago it was suggested that tuberculosis was so widespread that many, perhaps most of us, were immune from its infection because a former attack of the disease protected us.

Every argument I have yet heard or read of which is set up to support the theory of the existence of a peculiar heredity in connexion with tuberculosis seems to me to fall to pieces before the facts, which, I submit, prove that the incidence of tuberculosis depends upon infection of the individual and not at all upon any peculiar hereditary taint or tendency in him. So late in this discussion, I will not inflict upon you a repetition of the familiar arguments which a good many of us have already publicly stated against the belief in a peculiar heredity connected with the spread of tuberculosis.

Grant for one moment that it is true that there is a peculiar hereditary tendency to tuberculosis, and I would ask, What useful end does it serve in helping us to get rid of tuberculosis? I know of none. If it be true that many of us are protected—and I think it probable that, to some extent, we are protected—from a second attack of tuberculosis because we have already had that disease, of what use is that belief when we seek for weapons with which to fight a pest which kills about 50,000 people every year in England and Wales? Better far, in my judgment, is it to leave these theories for use in mere academic discussions, and for research workers who may show us good in them. But for present-day needs it is, I venture to say, our duty to drive home to our people what we know is true, and to impress upon them that tuberculosis is a curse which falls on man to the extent it now does only because he does not use to the full the help which medical science to-day offers. In the last thirty years the death-rate from tuberculosis has fallen from 25 to 10 in every 10,000 of the population. In very great measure we know how this has been done; but I have not yet heard of any useful contribution to that work which has come out of the theory that there is a peculiar heredity connected with the incidence of tuberculosis among men.

Mr. GEO. P. MUDGE[1] (London Hospital Medical College) said that in opening the discussion there was one point he would specially like to emphasize, and it was that, sooner or later, he supposed, circumstances would compel medical men to approach the study of human inheritance seriously. When they did that, the first question which they must necessarily ask of themselves was: which method would they employ? At the present time there were two Schools of Thought and of Method: and the medical profession, in accepting one of them, must inevitably reject the other. One of these was the School of the Ancestrians, or, as they preferred to be known, the Biometricians: the other School was the Mendelian. The former largely based their methods and results on the conception of continuous variations—*i.e.*, they believed that new species arose by the piling up in successive generations of what were termed continuous or fluctuating variations. This was nowhere more emphasized than in Professor Karl Pearson's work on the Shirley poppies, and it showed that Biometricians placed the greatest importance upon this conception of the evolution of species. The Mendelian School, on the other hand, took a different standpoint. While not

[1] Mr. Mudge reopened the discussion on December 2.

refusing to recognize that fluctuating variations existed and played a certain part in the phenomena of living organisms, they did not think they played an important or a large part in the evolution of species. On the other hand, they contended that the evidence justified them in believing that species had been evolved by the sudden origin of new characters. There was a prevalent idea abroad, and nowhere more manifest than in the Biometrical School, that necessarily these mutations or "sports" must be variations of large moment. This is not the Mendelian conception at all. A mutation might be of quite small moment, almost as small as the smallest fluctuating variation. Their contention is that a mutation, once having arisen, would breed true; and, so long as it did this, it might be either of large or of small moment. Fluctuating variations, however, did not breed true.

With regard to the methods, the Biometrician collected his material as best he could; his object was to get masses. That was emphasized by Professor Pearson's appeal to the meeting last time: "Pedigrees, more pedigrees." Having got these masses, the Biometricians proceeded to make the best of them, and he (Mr. Mudge) proposed to show how far they had succeeded and how far they had failed in their purpose. On the other hand, the Mendelian did not care much for masses as such, but he did care that he should have individual cases carefully studied and rigorously analysed. Having obtained a large number of clear analytical results, they could deal quite trustworthily with the masses thus obtained.

Turning now to the question of achievements, what had the two Schools done? The Biometrical School had been in existence a long time, but the Mendelian School had its birth only eight years ago. Already the Mendelians had practically revolutionized the possibilities of agriculture and cattle breeding. Taking the case of wheat, the agriculturist sought in one plant the characters of resistance to rust, large ears, strength of quality and capacity to ripen early. Until the Mendelian came this was not possible, but it will now be possible to combine these qualities by appropriate crossing and to obtain a stable race. What result to compare with that could the Biometricians show? He would mention another Mendelian accomplishment which was of great importance to medical men. Was there anything yet achieved in the Biometrical guild which would justify a medical man, in regard to the subject of marriage, advising his patient, as an individual, what he should do in certain given circumstances? He believed Professor Pearson would not be able to adduce a single such instance. But it was otherwise with the

Mendelian, and if he had succeeded in respect to one character, he was later going to succeed with others: it gave an indication of what is possible. Taking the case of brachydactyly, which had been investigated in the human subject by Dr. Drinkwater and by Mr. Farabee, a medical man could now confidently advise a patient in respect to it. Supposing a normal individual, who had the normal fingers, but one each of his parents and grandparents had been brachydactylous, came to a medical man and, explaining the circumstances, said he wished to know whether, if he married a normal person, any of his offspring would manifest the abnormal condition, what would the medical man be justified in predicting? There is always a certain amount of danger in making too confident a statement, but from the evidence one felt quite justified in predicting that the whole of the offspring from that person would be quite normal: that once the brachydactylous condition had disappeared it would not reappear. The Mendelian recessive would breed true. This was an instance of what could be done in practical life as the outcome of Mendelian work.

He would come now to the question of human albinism. Professor Pearson described the case of a normal woman who married two unrelated husbands, and in the offspring of both albinos had appeared. The Professor then went on to calculate the probability of the Mendelian explanation being correct. The Mendelian explanation is that this woman and both the husbands must be carrying albinism recessive. Professor Pearson said that if one knew the number of albinos in the country where this case occurred, they could calculate the probability of the woman meeting two husbands in succession in whom albinism was also recessive: he showed it, by the Theory of Probability, to be something very remote. The validity of that judgment wholly depended upon the geographical circumstances of the case; it depended on where the case occurred, and where the individuals in question came from. He hoped Professor Pearson would tell the meeting where they came from. [Professor PEARSON: Glasgow; two of them (the wife and one husband) were in Glasgow for generations, and one (the other husband) came from the Highlands.] This, at first, seemed to be against the Mendelian interpretation, since it occurred, not in a remote village where cousinship marriages are common, but in a large city; but it really is not so. He knew various villages and towns at different points along the whole west coast of Scotland as far as Portree in Skye, and albinism is fairly common in this region compared with its frequency elsewhere. He had

several pedigrees which he had collected, though they were not complete. Glasgow was naturally largely recruited from this west coast, and when one remembered that for every albino which occurred in this region there must be twice that number, and probably more, having albinism recessive, and that endogamy—marriage within a village—was, and still is, very common, so that cousins are very numerous, and that albinism is scattered over the region, the fact is not very startling. Recessive albinism on a relatively large scale must have been carried into Glasgow and Edinburgh for generations past. In fact, Professor Pearson's case is just what the Mendelian would have been led to predict, and it is very kind of him to thus confirm the Mendelian's prediction. And whereas the Biometric law of Ancestral Inheritance will not explain this case, he submitted that Mendelism is a very good explanation.

Professor Pearson has said there is every grade of albinism; now two conceptions hinged on so-called partial albinism. The Professor did not say what was the significance of these grades with regard to Mendelism: he left them to say for themselves, or to judge of it from his previously published works. Taking the Shirley poppy papers, where the author figured a large number of poppy petals, white at one end of the series and scarlet at the other, with every existing intermediate stage in between, Professor Pearson contended that the stages occurred without a break, and seemed to infer that it was a case of continuous variation. So judging by analogy, the albino appeared to be regarded by the Biometrician as the last stage in a graded series of reductions of pigmentation. He would be glad to know if Professor Pearson still accepted this conception. [Professor PEARSON said Mr. Mudge was not right, but he would not interrupt him.] Then the only alternative remaining to Professor Pearson is to accept the other conception—*i.e.*, that the varying degrees of pigmentation had come by separate mutations. If Professor Pearson accepted the mutational conception, the Mendelian School could congratulate itself upon having made a very renowned convert. But perhaps he did not wish to say just now which conception he preferred. [Professor PEARSON: Will Mr. Mudge define an albino?] An albino is an organism in which there is complete absence of pigmentation other than the blood and bile pigments. Perhaps Professor Pearson would now answer his question as to which conception of the nature of intermediates he accepted. [Professor PEARSON said he did not at all necessarily regard the degrees of pigmentation as stages through which the albino passed in the course of

evolution. What he said was that it was very difficult in a given individual to say whether it was or was not a complete albino.] Mr. Mudge, continuing, said that even then he did not see why Professor Pearson persistently emphasized the existence of "all possible grades," and in such a controversy it is very desirable to nail one's colours to the mast. The Mendelian is prepared to do so, and to say that the evidence justifies us in tentatively believing that the albino came out of a wholly pigmented stock as a sudden sport or mutation, and that it had not passed through these graded stages. If Professor Pearson has now abandoned this latter conception of passage through graded stages then he had come over into the Mendelian camp.

He would pass on to consider the nature of this partial albinism, as the Professor called it. He (Mr. Mudge) took exception to the term "partial albinism." He did not regard the partially pigmented individuals as albinos at all; they have nothing to do with albinism; they are simply pigmented individuals in whom the amount of pigment has been reduced. In the lower forms of life there are perfectly stable and normal types in which the pigment is reduced: rabbits, guinea-pigs, rats, and mice. And, on the one hand, there are individuals that are wholly pigmented at one extreme of the scale, and at the other there are complete albinos. Were they dealing with cases of the same stable and normal nature in human so-called partial albinos? He thought it probable that they were not. There are three biological considerations which he did not think Professor Pearson had given sufficient attention to with regard to human albinos. First, that of arrested development, such as, in other directions, is indicated by hypospadias and imperfectly descended testicles. When certain of the lower animals, such as rats, mice, guinea-pigs and rabbits are born, they have an incomplete condition with regard to pigmentation; the eyes are pigmented, but the skin is pigmentless. If we supposed some of them failed to develop pigment in their skin they would grow up albinos with regard to their bodies, but have pigmented eyes. They would then be called partial albinos. That is what is seen in many so-called partial human albinos, but they are not albinos of any degree; there is something abnormal about them. The frequent association of these types with nervous disorders suggests they may be even pathological. Many human babies have, at birth, blue eyes and fair hair, but later a large number of them have brown pigment in their eyes, and their hair becomes dark. But if we supposed the baby stopped short at the earlier condition it would not be a case of albinism, nor even of a partially pigmented

organism, but an arrest of normal development of pigmentation. Among lower forms a similar change of colour occurs after infancy. As a personal observation, he (Mr. Mudge) can testify that grey rats, a short time after birth, are black and not grey. The grey colour came later, shortly after the hairs appeared. Mr. C. C. Hurst has observed the same thing with grey rabbits. Should something inhibit the second stage, these animals would appear black, and yet be potentially grey. He once had in his possession (December, 1905) an axolotl which would have been called a partial albino, and it manifested some of the phenomena shown by human partial albinos, for it became more extensively pigmented as time advanced. It was quite white, with the exception of the black eyeballs. At the end of four weeks after it was first purchased, the dorsal surface of its external gills developed a small amount of dark pigment. Within the next few weeks this increased in quantity, and the dorsal surface of the head and of the front end of the trunk began to be darkly pigmented. The animal died at the end of the eighth week, but it is possible, had it lived, that it would have become wholly pigmented. This increased pigmentation cannot be explained by increased illumination, for it was kept in a badly-lighted part of the laboratory. Such an individual cannot be regarded as an albino, nor even as a stable type of reduced pigmentation analogous to a piebald rat. It is best described, though not explained, as a case of temporarily arrested development. It is very similar to many of the cases of human partial albinos. That seemed to him might be the case with regard to some or all of the intermediate grades of albinism in man with which Professor Pearson dealt. In a large number of cases of partial human albinism, when the individuals were born they were much less pigmented than afterwards, when pigment later developed in eyes, hair and skin, but they never became normal, though in one or two cases they approached normality. They could not be considered stable products, but as individuals in whom development had suffered arrest. And conversely it is known that pigmented individuals might, at some period of their lives, lose some of their pigment, producing what was admittedly a pathological condition called leucoderma; piebald people with colourless patches over their bodies were examples. These people, too, have been called partial albinos. Professor Osler had told him that such people were very common in America among the negroes. But they were not comparable with the stable varieties of parti-coloured organisms. In lower forms there is no correlation between reduced pigmentation (stable piebald forms) and nervous instability. But in man this appears

frequently to be the case. So if Professor Pearson bases his views upon these cases of human partial albinos and he regards them as stable natural products, he is probably going along a wrong line of thought.

But even if we choose to regard these human partial albinos as stable and normal types (and it is conceivable that such may exist even in Man, though their existence is not yet demonstrated), they are in no way inconsistent with or fatal to the Mendelian principles. As stable and normal types, only two conceptions of them are possible. Either they are fluctuating variations and represent the stages through which the complete albino has been evolved from a pigmented stock—they are the steps of the evolutionary staircase, down which the albino has passed—or they are discontinuous variations, and each grade represents a distinct mutation, which breeds true to itself within the limits of its individual variation. Professor Pearson has declined to nail his colours to the first of these conceptions—the one upon which his past work has been largely based—and if he accepts the latter, then he has passed the frontier, and is already in the Mendelian School as a convert from the other.

He (Mr. Mudge) did not know of any evidence that partial albinism in man had arisen as a mutation; but in the lower animals, and in plants, there are some very remarkable cases of mutations in diverse characters. There is the one which Professor Bateson pointed out at the British Association in 1904. It is in connexion with the sweet-pea flower. From the pea to man is a far cry, but he (Mr. Mudge) would endeavour to show what relation lower forms generally bore to man. Among sweet-pea plants there are, at one end of the scale, a purple-flowered one, and at the other end an albino-flowered one. Between these two extreme types are a number of different shades of colours which form a graded series. The idea of the Biometrical School with regard to these, judging by the "Poppy" paper, is that they are continuous variations, indicating the stages through which the albinism arose by a series of successive reductions in the course of its evolution from the purple-pigmented flower. But there happens to be a history of these coloured races of peas, and it is very instructive to both biologists and medical men. It is known that the white flower arose long before any of the intermediate grades, and it must, therefore, have arisen as a "sport" or mutation from a purple parent. The intermediate grades were subsequently and independently evolved. So the idea of continuous variation and the evolution of new races by breeding from the most extreme of these fluctuating variations, in each

generation, is not justified by the facts. If that were so in plants there is no reason for supposing that, when full evidence is obtained, it would be otherwise in man. There is no adequate reason to believe that the processes of Nature are different for man than for lower forms of life. To take another case of a mutation the history of which is known. It is recorded that a dwarf bean plant[1] about 1 ft. high suddenly arose from a tall bean plant which is about 6 ft. high. As an example of a rather more complex mutation there is the case among animals which Darwin alluded to—*i.e.*, the Ancon race of sheep which is now no longer bred. It was characterized by a very long body and short legs. This race arose from a single mutant ram lamb in 1791, which took its origin out of normal parents. A few years later (1828), in France, another mutation, also among sheep, occurred. The ordinary hair of sheep is fairly short and very wavy. From a pair of ordinary parents having merino wool of this sort there arose a ram lamb whose hair was very long and straight, much smoother, and silky to the touch. These three mutations arose simultaneously, and they were all of small moment. They were not preceded by any intermediate conditions. In this case the same mutant individual simultaneously manifested other mutations —*i.e.*, a small stature, large head, long neck, narrow chest, smooth horns. The existence of such mutations as these shakes the basis upon which Biometry has been reared. Every example of a mutation which occurs in Nature is a brick in the edifice of Mendelism and is a clod of earth dug out of the grave that is preparing for the Biometrician. Coming to man, one saw similar remarkable mutations, and medical men will recall examples of cleft palate, hare-lip, microcephalic idiots, club-foot, hæmophylia, and alkaptonuria. The histories of these are not recorded; it is only known that they have arisen. But there is good ground for believing that they are of the same nature as those he had mentioned in lower animals. This indicates something of the profound importance which a study of lower forms possesses for the medical man. He would give one more case of a mutation, because it is one which has bred true for a large number of generations. All the tabby cats in London could be put into two groups: one with a generally single line running down the middle of the back, and stripes passing off vertically outwards over the side. This may be called the striped tabby. In the other group there are usually three stripes down the middle, and the lateral stripes pass off obliquely backwards, the main ones being thrown

[1] *Phaseolus lunatus.*

into characteristic and more or less looped curves. This is named by Mr. Reginald Pocock the blotched tabby. A photograph of each of these types is shown in figs. 1 and 2.

There is something to occupy Professor Pearson's spare moments. The Biometricians might be usefully employed in seeking to find intermediate stages between these two types of tabby cats. Yet they had been breeding promiscuously together in London ever since the sixteenth century. Not only is this a case of mutation, but—what is more important in the present controversy—there is perfectly clear

FIG. 1.
The striped tabby. (From the *Proc. Zool. Soc.*, 1907.)

and incontrovertible evidence of segregation and of gametic purity. The tabby cats give a clear case for Mendelism, which is based upon two fundamental conceptions: (1) segregation of alternative characters in the gametes; that is, they do not blend but remain quite distinct; (2) and gametic purity—that is, the two alternative characters are carried in different sex-cells of the individual. Segregation alone would not enable us to explain the facts of this case. There must be gametic

purity as well. He invited Professor Pearson and his disciples to carefully consider the case of the tabby cats, how they segregated and carried pure gametes. [Professor PEARSON: Have you the ratio of the two types of tabby cats to the whole number?] Mr. Mudge: No. My statement is based upon Mr. Reginald Pocock's observations as described in his paper,[1] and no breeding experiments have yet been undertaken. But ratios are not at all necessary to demonstrate segregation and gametic purity. I am concerned now in calling attention to the existence of these phenomena and to the fact that since no intermediates exist the two types of tabby markings must be regarded as having arisen

FIG. 2.

The blotched tabby. (From the *Proc. Zool. Soc.*, 1907.)

by mutation. If Professor Pearson has an alternative theory which will explain this case of the tabby cat, everyone will be delighted to hear it. Brachydactyly, again, presents no intermediate stages; it is a human mutation and follows the Mendelian processes of inheritance.

He next wished to consider the biometric methods as far as they can be legitimately judged by their results. He was not prepared to pass a verdict upon biometric methods by an examination of the methods

[1] *Proc. Zool. Soc.*, 1907.

themselves. But that is not necessary; the results are sufficient, for if these are erroneous, the methods cannot be right ones. Professor Pearson has said that the albino pedigrees which he possesses fail utterly to support Mendelism. Such statements with regard to Mendelism have been uttered by Professor Pearson before on more than one occasion. But subsequent investigation has never confirmed them, and it is highly probable that future research will equally fail to corroborate this present utterance. He (Mr. Mudge) proposed to consider some of these past utterances. He would not misquote the Professor, and he would read his exact words from an article dealing with eye-colour in man. In *Biometrica*, ii, p. 213, Professor Pearson wrote[1]: "No single colour breeds true to itself," and again on p. 215, "nor again do we find that two black-eyed human beings, nor two blue-eyed human beings, mated together give any sign of the dominance of one or other of these extremes." Then the Professor gave, on pp. 214 and 215, what he supposed was intended to be the scorpion's sting and the fatal thrust: "Nothing corresponding to Mendel's principles appears in these characters[2] for horses, dogs or men." These were perfectly definite statements, from which Professor Pearson could not escape. But it so happened that eye-colour in man has been subsequently investigated; in England by Mr. Hurst, and in America by Professor Davenport; and he (Mr. Mudge) had brought some of Mr. Hurst's tables (Tables I to III, pp. 128 to 130) to show the results and conclusions of their work. Taking the first statement, that no single colour breeds true to itself, he showed the result of Hurst's investigation of the inhabitants of a Leicestershire village. There are two groups of eye-colours. One group contains all the eyes which are more or less dark, and which possesses brown and yellow pigment, which Hurst calls "Duplex." The second group contains all the pure blue eyes—*i.e.*, those without visible yellow or brown pigment, and which he calls "Simplex." In the Simplex eye the pigment[3] which produces blue colour is contained at the back of the iris; in the Duplex the blue pigment is also present, but in addition there are brown and yellow pigments in the front of the iris. And the general result of this investigation shows that the Duplex eyes are dominant over the Simplex. It therefore follows as a logical corollary, from the Mendelian standpoint, that the blue eyes, once they are separated out, should breed true, and there should not be any brown eyes in their progeny. In

[1] "The Law of Ancestral Heredity," *Biometrica*, 1902-03, ii, p. 211.

[2] Coat-colour in horses and dogs and eye-colour in men.

[3] It is really a purple pigment, but appears blue when seen through the tissues of the iris.

that village there were 101 children as a result of Simplex and Simplex matings (Table I), and all showed the Simplex eyes—*i.e.*, with blue irides. So, on that very definite and comprehensive statement of his, Professor Pearson was unconfirmed by the facts of this case. But care must be taken that the blue eyes chosen are actually blue eyes, because some supposedly blue eyes are not so in fact, as they contain a small quantity of visible brown pigment in front of the iris, which may be very easily overlooked. Mr. Hurst calls attention to this point in his paper. Professor Davenport, at the same time in America, independently corroborated this result, and showed that the recessive blue character mated to the blue bred true. If we turn next to the dark-eyed character, we find that Mr. Hurst's results show that if an impure dominant is taken—*i.e.*, one which carries the Simplex character recessive, and it is mated with a recessive, one expects, in accordance with Mendelian principles, to get an equal number of dark-eyed people with the blue-eyed people. The table (III*b*) exhibited shows that they are approximately equal. The expectation is 129 : 129. The actual result is 121 : 137. If the dominant parent were a pure dominant (did not carry Simplex recessive) then all the offspring is expected to be Duplex. Table III*a* shows an offspring of this type, and effectually controverts Professor Pearson's statement that no eye-colour is dominant. If one took two dark-eyed parents, the dark-eyed condition being dominant, further complexities are introduced. These complexities arise from the fact that three kinds of matings are possible between dark-eyed parents. If D stands for the dominant character (dark-eyed condition), and R for the recessive or blue-eyed condition, we can symbolically represent these three matings and their results as follows :—

Parents		Nature of expected offspring
(1) DD × DD	=	All DD
(2) DD × DR	=	1 DD + 1 DR = all visibly D
(3) DR × DR	=	1 DD + 2 DR + 1 RR = 3 visibly D + 1 R

So far, therefore, as *visible* characters are concerned, we expect one of two results in the offspring of two dark-eyed parents. Either all the children will be dark-eyed (1 and 2) or some will be dark-eyed and others blue-eyed, and the former should be in a large majority (3). The Tables (II*a* and II*b* and III*a* and III*b*) which are exhibited, and which are copied from Mr. Hurst's Royal Society's paper, show the result of these different matings. Table II*a* shows the offspring of marriages which illustrate matings of types 1 and 2, where the

offspring are all duplex-eyed. Table II*b* gives the mixed offspring arising from marriages of the third type of mating; and here the Mendelian expectation in nearest round numbers is sixteen Simplex, forty-seven Duplex. The result is 18:45 respectively.

Hurst's results, therefore—and the same may be said of Davenport's results—come out in accordance with the Mendelian explanations, not only qualitatively but quantitatively. This, it seems to me, effectually disposes of the statements in *Biometrica* regarding eye-colour in man. And this consideration introduces a very serious question for Biometry, because if that system, with all its putative refinement of analysis, gives such misleading, and even false, conclusions, the sooner it is discarded for something more appropriate to the conditions of biological problems the better it will prove for the advance of medical knowledge. But Professor Pearson has made a precisely similar statement regarding the transmission of coat-colour in horses. He (Mr. Mudge) would again quote from the same work[1]: "It is the same with every coat-colour taken. Its relative constancy depends largely on the extent to which it has appeared in the ancestry, and one by one black, bay, chestnut, grey must be dismissed by the Mendelian as neither 'recessive' nor 'dominant,' but as marking permanent and incorrigible mongrels." "It is just worth reiterating that nothing corresponding to Mendelian principles appears in eye- and coat-colour for horses, dogs and men."

Once more an appeal to facts lends no support to Professor Pearson's statement. It is a point of some interest and significance to note that in regard to eye-colour in man, the Mendelians had a different set of data from those which were the basis of Professor Pearson's conclusions, but in regard to horses the same data were used, so that any difference in the conclusions arrived at depend not upon the material used but upon the validity and accuracy of the methods of analysis employed. This case is, therefore, a test of the accuracy of the two Schools of Method. Let us turn to the facts. Hurst found there is a colour which breeds true to itself, and this colour is chestnut; for he found that chestnut is recessive to bay and brown, and when extracted from brown or bay parents, and is mated with chestnut, only chestnut offspring result. Hurst has produced, from Racing Calendars and Stud Books, 1,104 cases of chestnut foals which have been born from chestnut parents, but it is only fair to say that there are nine exceptions. When these are carefully examined, however, it is found that they are due to

[1] *Biometrica*, 1902-3, ii, pp. 214-215.

want of care in the pedigrees which are kept by the horse-breeders, and the breeders have admitted that they alter their records, both in the Racing Calendars and in their Stud Books. It is known, with regard to some of these exceptions, that horses which are really chestnut and were so entered in one book were in the other book described as bay or brown. Thus those nine exceptions are of no significance. Mr. Hurst further showed that when the bays and browns are crossed with chestnuts two results are obtained: either all the offspring are bays and browns or 50 per cent. are chestnuts and 50 per cent. bays and browns, chestnut being recessive to bay and brown. This result is precisely what the Mendelian predicts—*i.e.*, that the individuals manifesting the dominant character will be one of two things: either pure dominants or impure dominants carrying chestnut recessive. In this latter case, when bred with chestnuts, they will give 50 per cent. chestnuts; and in the former case none. In view of these results in human eye-colour and in coat-colour in horses, he asked the meeting to accept with considerable reservation the statement of Professor Pearson that there is nothing in the pedigrees of human albinos to give support to the Mendelian theory. For it is quite certain, judging by past results, that they may be wholly Mendelian in their manifestations and yet, owing to the inapplicability and crudeness of Professor Pearson's methods, they would not be revealed as such. He asked for a suspension of acceptance of Professor Pearson's statements until the Mendelians had further investigated the question and had a fuller opportunity of analysing Professor Pearson's records.

He (Mr. Mudge) would not, however, be satisfied with the position already reached if he could be allowed to very briefly refer to a case of albinism among negroes given by Mr. Farabee. As far as the author had given an account of the matter, it appeared that the grandmother was a normal negress, the grandfather an albino negro. Their offspring consisted of three fully pigmented negroes. Two of them married normal negresses, and had all black offspring. But one twice married, and in each case his wife was a normal negress (fig. 3). It is a case, in fact, very similar to the Glasgow one of Professor Pearson, and his case should be read in the light of the facts of this one. By each of these two wives he had some albino children. What is the Mendelian expectation in this case? Clearly, this husband must himself have carried albinism recessive; we know this from his parentage, and his two wives, it must be assumed, also carried albinism recessive.

Now what is the justification for this assumption? It is twofold.

Careful experimental observation on animals and plants has shown us conclusively that albinos can only appear in an offspring from pigmented parents when both of them carry albinism recessive. In this case we know, as a matter of fact, that one of the coloured parents must have carried it, because it came in with his parentage, and in the light of observed facts we are justified in deducing its existence in the other. In the second place, it has already been pointed out that for every albino seen there must exist twice or more that number of individuals carrying albinism recessive. For it must be remembered that visible albinism in one individual is the expression of recessive albinism in two parents, and that from such parents, for every albino child born to them there will, on the average, be born to them also two in which it is not patent, but recessive and invisible. Therefore, in any community containing albinos there must exist twice that number of individuals with recessive albinism. Now, what are the facts of population with regard to Farabee's case? Farabee tells us that in addition to the particular

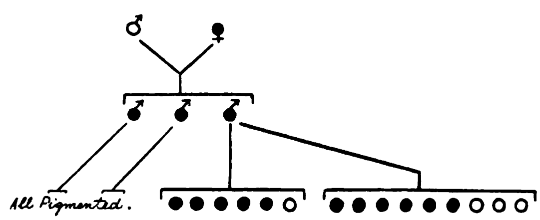


FIG. 3.

Mr. Farabee's case of albinism in negroes. The sex and age of the children of the present generation are not stated. Solid black symbols represent the normal or pigmented negroes, and the ringed symbols the albinos.

albinos which we are now considering, " there are others in the vicinity." In this locality[1] there are a number of albinos, and it is therefore highly probable—indeed, almost certain—that there exists twice that number of coloured individuals with albinism recessive. The assumption, therefore, is not only warranted by the facts, but we are almost left with no alternative but to make it. The considerations which he (Mr. Mudge) urged for this case, he would also urge as being applicable to the Glasgow case cited by Professor Pearson. The probability which Professor Pearson calculates as remote is not so, but is highly imminent. The processes of life are too complex and too subtle to be effectually dealt

[1] Coahoma County, Mississippi.

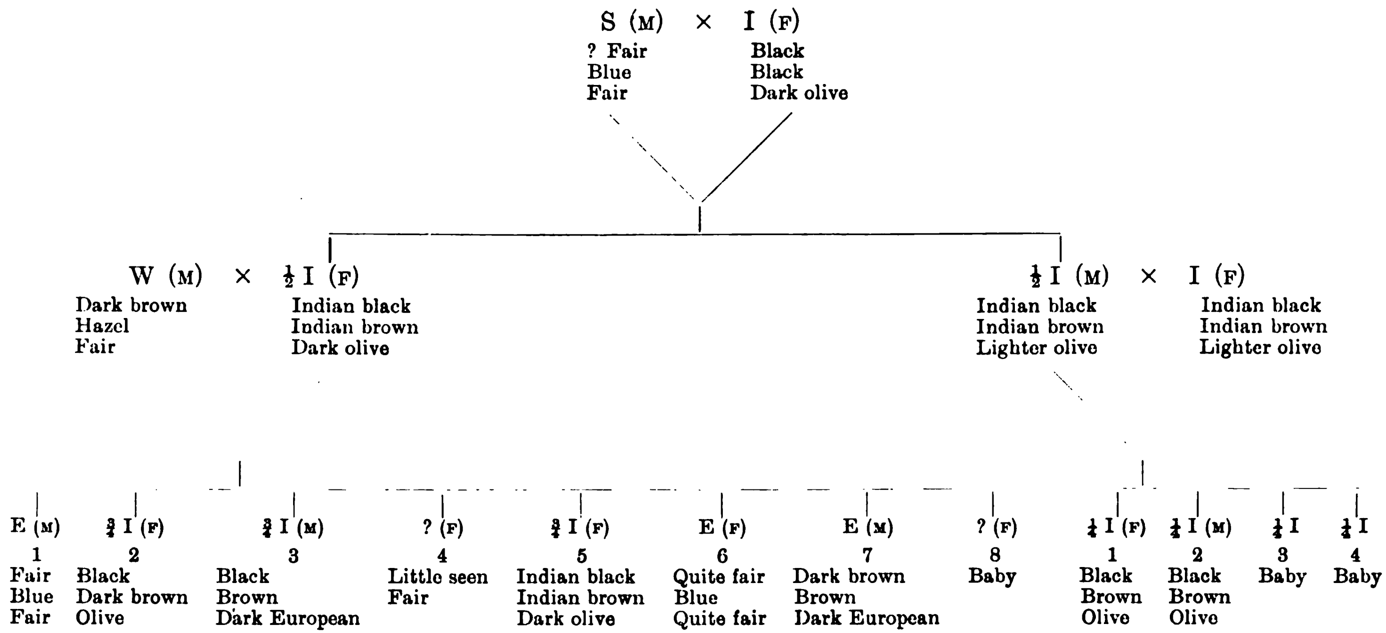
with by the crude massing of biometrical methods, or by a "Probability" formula. Living gametes and living zygotes are not dead marbles shaken up to a uniform distribution in an equally dead bag.

With regard to the quantitative result in this case, what is the Mendelian expectation with respect to the offspring of the negro who married twice? There is a total offspring of fifteen. In nearest round numbers, the expectation is eleven pigmented individuals and four albinos. The actual result is eleven pigmented and four albino individuals. Mendelian expectation and result are thus coincident for albinism in man, as they are for similar cases in lower animals and plants. There is in this case, as in eye-colour for man, clear evidence of segregation and gametic purity.

He (Mr. Mudge) would now like to describe another case of the segregation of normal human characters. This case has not yet been fully published, and it deals with the offspring resulting when two distinct races are crossed. He is at present collecting further information with regard to these crosses. The races of mankind now under consideration are Europeans and the Red Indians of North America. He would for present purposes only describe one case (fig. 4). It is that of an old Hudson Bay factor, a Scotchman, whose hair was said to have been fair,[1] eyes blue and complexion fair. He married a full-blood Indian woman, with Indian black hair, Indian black eyes and Indian olive complexion. There were two children by the marriage—a son and a daughter. Both of these were Indian with regard not only to the three characters now under consideration, but in other facial features too. The son, however, was rather a lighter shade of olive in complexion than the daughter. The half-breed son married a full-blood Indian woman and had four children—a son, a daughter, and two babies whose sex were not ascertained. The son and daughter were Indian in all three characters—*i.e.*, hair-colour, eye-colour, and complexion.

The marriage that interests us most is that of the half-breed daughter with a Welshman. He had dark brown hair, hazel eyes, and fair complexion. In connexion with his characters it must be remembered that hazel ("Duplex") eyes can carry blue ("Simplex") recessive, and Mr. Hurst tells me that he has evidence that dark-haired individuals can carry the light-haired character recessive. If this Welshman is a heterozygote (an impure dark European, carrying lighter features recessive) then, bearing in mind that his half-breed Indian wife is the

[1] It is now white through age. The person is over ninety years of age.



S = Scotchman W = Welshman I = Full-blood Indian ½ I = Half-breed Indian E = Of European aspect in regard to characters considered (F) = Female (M) = Male

FIG. 4.

EUROPEAN AND NORTH AMERICAN RED INDIAN CROSS.

Three characters are considered, and their nature is stated under each individual. The characters in the order arranged are: hair-colour, eye-colour, and complexion.

The author is indebted to Mr. Gerald Hoole for this pedigree. He lived for many years among the Indians of the North-West, and intimately knew all the people concerned.

daughter of a fair-haired, blue-eyed, fair-complexioned Scotchman, it is expected, on Mendelian principles, that the blue eyes, fair complexion, and light hair shall reappear in his offspring. And the pedigree shows that it does actually reappear in the F2 generation among the Welshman's children, for of the eight children, two (Nos. 1 and 6)—a son and a daughter—have fair hair, blue eyes, and fair complexion. It would be difficult to conceive of a clearer case of segregation and gametic purity than this. It is impossible to confound the three extremely fair European facial traits which we are now considering, and which were manifested in the Scotchman and must have been carried, as we know they can be carried, in the type of European exemplified by the Welshman, with the corresponding very dark features of the full-blood and half-breed Indians. The transmission of other facial traits, such as the high cheek-bones of the Indian, does not concern us; but it may be well to mention that both these children (Nos. 1 and 6) exhibited high cheek-bones, not so pronounced in No. 6 as in No. 1. These results are entirely Mendelian, and are precisely those which the Mendelian would expect. It should not, however, be thought that the problem as a whole is as simple as it may appear to be from the particular case chosen. The problem is, as a matter of fact, more complex than it appears. It cannot be adequately discussed until we know what pigments and ferments are present in Indian and European skins respectively, and he (Mr. Mudge) is at present endeavouring to obtain pieces of Red Indians' skin for analysis.

He would, in conclusion, take one more case. He was indebted to the kindness of Dr. Drinkwater for permission to describe it. It is one of Dr. Drinkwater's hitherto unpublished cases. It is a case of congenital asthma. It is quite Mendelian in that the affected persons transmit the disease and the unaffected do not. It is Mendelian, too, in that some individuals are asthmatic and the others are quite normal. The proportions of asthmatic and normal individuals in the descendants of parents, one of whom in each pair is asthmatic and the other normal, is that predicted by Mendelian principles (fig. 5). An equal number of each is expected, and if we assume that the original pair (of whom there is no record) consisted of a normal and an abnormal member, then there are ten asthmatic and ten normal descendants. Looking at all these cases and bearing in mind the considerations which have been urged, Professor Pearson's very comprehensive statement that there is no evidence for Mendelism becomes as incomprehensible as it is unjustified.

Professor Pearson concluded his opening speech by an appeal; he said a wave of inquiry was wanted in the medical profession. With that he (Mr. Mudge) agreed; and when Professor Pearson further said that more pedigrees are required, he also agreed. But he did not agree that, having obtained these pedigrees, they are all that are required. If, for instance, 10,000 pedigrees of hæmophilia were obtained he did not think they would have attained the full measure of truth until the physiological chemist and the pathologist came to their help. It is necessary to know what are the factors, or absence of factors, which are concerned in the production of hæmophilia. He entirely dissented with the view implied by Professor Pearson that the pedigrees, when obtained, should be passed over to the biometrician for biometrical treatment, and he threw down a challenge to that School to show that their methods were able to extract not only the best, but even the core of truth, out of the material. He had already shown that Professor Pearson's methods gave false conclusions. There is at present no better method than that of the Mendelian; it is the method of accurate experiment and the analysis of individual cases.

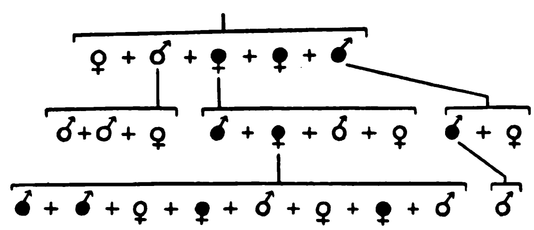


FIG. 5.

Dr. Drinkwater's case of congenital asthma. Solid black represents the affected and the ringed symbols the unaffected.

Professor Pearson has assured us that Biometry is destined to convert Biology into an exact science and to effect the salvation of biologists from the alleged perdition of theory, hypothesis, random speculation, and vague terminology into which they had drifted before the biometrical angel had outspread her wings and come to earth to guard them and to lead their erring footsteps along a better road. But if one went through the "Grammar of Science," a very modest book which was written by Professor Pearson to give instruction in the elementary principles of Biometry, and read especially pages 437, 446, 451, 458, and 461, one

found that the biologist's younger brother's mote was very big, for assumption upon assumption, inference upon inference, and hypothesis upon hypothesis is interwoven and incorporated into the fabric of Biometry. One of these theories is that of Gauss-Laplace, and it is a theory of deviations. This theory constitutes the base of the biometrical method of the correlation tables, and these tables constitute the one instrument of inquiry by which the biometrician approaches questions of inheritance. Biologists decline to accept that theory as being legitimately applicable to living organisms. It should also be observed that it, itself a theory, is based upon three hypotheses, neither of which is accepted by biologists as being true of living things.

Biologists can only judge the value of Professor Pearson's methods by the results they give. If his results are inconsistent with those obtained by purely biological methods, they cannot be accepted. Biometrical *methods* are based, as already shown, upon assumptions; biological methods are not. They are the methods of observation, of experiment, and of verification. They do not involve, as biometrical methods do, the rejection of beech leaves with too many veins and of those with too few veins. They do not involve the collection of data upon the basis of false premisses, rendering it necessary to pick and choose in compliance with these premisses. Such methods introduce errors that have multiplied and remoter consequences, in addition to the immediate ones, for upon the conclusions deduced from the results of their application other premisses and other conclusions are later based. The foundation-stone of the biometrical method of the correlation table is unsound, and the superstructure that is being reared upon it cannot endure.

But while biologists cannot judge Professor Pearson's methods upon their intrinsic worth and apart from their results, there are mathematicians who are qualified to do so, and have in fact done so. It is only necessary to recall the heated controversy between Professor Pearson and Professor Kapteyn a few years ago, in reference to some of the methods of Biometry, to make it imperative upon biologists and medical men alike to pursue their own problems by the application of their own methods, which have accomplished our present results and which are the best guarantee for the attainments of the future.

TABLE I.—HUMAN EYE-COLOUR. SIMPLEX × SIMPLEX.

Initials of male parent		Duplex		Simplex		Total offspring
A. F.	...	0	...	4	...	4
J. T.	...	0	...	12	...	12
D. N.	...	0	...	11	...	11
J. M.	...	0	...	3	...	3
S. H.	..	0	...	3	...	3
F. G.	...	0	...	12	...	12
H. C.	...	0	...	6	...	6
J. L.	...	0	...	7	...	7
T. S.	...	0	...	4	...	4
E. D.	...	0	...	2	...	2
W. D.	...	0	...	4	...	4
J. C.	...	0	...	7	...	7
J. A.	...	0	...	4	...	4
J. D.	...	0	...	2	...	2
W. K.	...	0	...	5	...	5
A. B.	...	0	...	7	...	7
J. F.	...	0	...	2	...	2
J. H.	...	0	...	2	...	2
J. C.	...	0	...	2	...	2
A. A.	...	0	...	2	...	2
20		0		101		101

(Hurst.)

TABLE II.—HUMAN EYE-COLOUR. DUPLEX × DUPLEX.

(*a*) Giving all Duplex.

Initials of male parent		Duplex		Simplex		Total offspring
W. H.	...	8	...	0	...	8
J. C.	...	2	...	0	...	2
T. S.	...	8	...	0	...	8
J. P.	...	6	...	0	...	6
W. H.	...	7	...	0	...	7
G. L.	...	6	...	0	...	6
J. B.	...	10	...	0	...	10
J. B.	...	3	...	0	...	3
C. B.	...	12	...	0	...	12
J. F.	...	7	...	0	...	7
B. H.	...	5	...	0	...	5
R. E.	...	6	...	0	...	6
A. S.	...	6	...	0	...	6
T. C.	...	9	...	0	...	9
J. W.	...	3	...	0	...	3
W. P.	...	4	...	0	...	4
H. E.	...	5	...	0	...	5
C. H.	...	6	...	0	...	6
J. S.	...	4	...	0	...	4
J. W.	...	8	...	0	...	8
J. G.	...	6	...	0	...	6
T. W.	...	4	...	0	...	4
J. B.	...	3	..	0	...	3
M. C.	...	2	...	0	...	2
W. P.	...	2	...	0	...	2
J. M.	...	5	...	0	...	5
B. B.	...	10	...	0	...	13
F. S.	...	2	...	0	...	2
E. G.	...	4	...	0	...	4
T. R.	...	2	...	0	...	2
C. W.	...	3	...	0	...	3
H. G.	...	4	...	0	...	4
G. K.	...	4	...	0	...	4
G. G.	...	3	...	0	...	3
J. R.	...	5	...	0	...	5
W. P.	...	3	...	0	...	3
A. P.	...	8	...	0	...	8
37		195		0		195

TABLE II—(*continued*).

(*b*) Giving Duplex and Simplex.

Initials of male parent		Duplex		Simplex		Total offspring
W. S.	...	1	...	1	...	2
J. W.	...	2	...	1	...	3
T. B.	...	3	..	1	...	4
E. E.	...	5	..	1	...	6
G. B.	...	5	...	1	...	6
J. R.	...	5	...	1	...	6
E. H.	...	2	...	1	...	3
H. H.	...	6	...	2	...	8
A. F.	...	3	...	2	...	5
J. M.	...	4	...	2	...	6
A. N.	...	3	..	3	...	6
E. D.	...	3	...	1	...	4
W. W.	...	3	...	1	...	4
13		45		18		63

(Hurst.)

Duplex-Simplex Matings.

The 69 matings of Duplex and Simplex parents also gave two kinds of results: (*a*) 17 families produced 66 offspring, all of the Duplex type; (*b*) 52 families produced 258 offspring, of which 121 were Duplex and 137 were Simplex.

Table III (*a*) and (*b*) give the numbers found in each family.

TABLE III.—HUMAN EYE-COLOUR. DUPLEX × SIMPLEX.

(*a*) Giving all Duplex.

Initials of Male parent		Duplex		Simplex		Total offspring
S. E.	...	2	...	0	...	2
J. H.	...	8	...	0	...	8
D. A.	...	2	...	0	...	2
J. H.	...	9	...	0	...	9
M. G.	...	3	...	0	...	3
L. C.	...	4	...	0	...	4
E. R.	...	3	...	0	...	3
W. D.	...	4	...	0	...	4
W. B.	...	2	...	0	...	2
T. C.	..	7	...	0	...	7
J. B.	...	5	...	0	...	5
E. A.	...	3	...	0	...	3
W. B.	...	4	...	0	...	4
J. H.	...	2	...	0	...	2
J. K.	...	2	...	0	...	2
H. C.	...	3	...	0	...	3
J. T.	...	3	...	0	...	3
17		66		0		66

(Hurst.)

TABLE III—*(continued).*

(*b*) Giving Duplex and Simplex.

Initials of Male parent	Duplex	Simplex	Total offspring
C. H.	3	2	5
G. F.	0	6	6
W. E.	3	5	8
W. J.	1	1	2
F. B.	3	1	4
J. B.	4	5	9
T. P.	0	4	4
R. B.	2	3	5
A. F.	5	5	10
R. C.	3	4	7
S. E.	4	2	6
J. S.	3	3	6
T. K.	2	2	4
G. D.	1	2	3
T. C.	5	1	6
T. L.	4	5	9
J. A.	2	3	5
W. W.	4	3	7
J. B.	5	4	9
J. R.	4	5	9
C. C.	5	4	9
W. P.	1	1	2
J. T.	2	4	6
G. S.	3	1	4
H. T.	1	4	5
W. R.	5	2	7
J. M.	3	3	6
W. N.	1	1	2
T. L.	3	3	6
W. H.	4	1	5
W. H.	3	3	6
D. S.	4	3	7
J. C.	2	3	5
G. G.	1	1	2
W. E.	1	1	2
R. S.	2	3	5
R. A.	1	1	2
G. K.	2	4	6
T. C.	1	2	3
J. P.	3	1	4
J. P.	1	1	2
A. P.	1	2	3
J. L.	1	1	2
C. H.	3	1	4
J. N.	1	2	3
J. B.	0	4	4
J. R.	2	3	5
J. F.	2	1	3
J. H.	0	2	2
A. B.	2	3	5
J. P.	2	1	3
E. C.	0	4	4
52	121	137	258

(Hurst.)

These tables are copied from Mr. Hurst's paper in the *Proc. Roy. Soc. Lond.*, 1908, lxxx, pp. 85-96.

Professor KARL PEARSON said he feared he had a very strenuous attack to answer without preparation, and he must carry the war largely into the enemy's camp. He could endorse heartily one only of Mr. Mudge's suggestions—namely, that those present should read the "Grammar of Science"; he was glad to say that he received a royalty on every copy sold! Biometry was neither Mendelism nor any other formal "ism"; it neither pledged itself to "mutations" nor to continuous variation; it was solely an attempt to apply exact methods to vital statistics of any kind. Biometricians complained that in nine cases out of ten Mendelians had not an elementary knowledge of how to deal with numbers, yet that knowledge was fundamental even to demonstrate Mendelism. To give an illustration of what he meant: suppose an experiment be made on, for example, the coat-colour of rats. The Mendelian expectation was, say, 1 in 3, but the numbers actually found 1 in 4. Did that prove or disprove Mendelism? No one could say unless he had studied the theory of statistics and knew the probability or improbability of such a result in a random sample of the given size. The Mendelian, looking at 1 in 4, said it was not quite good, so what did he do? He hunted up some other experiments, which were made twenty-three years ago on the same subject, in which the ratio given was 1 in 2. Then he puts the two together and divides by 2:—

$$1 \text{ to } 4 + 1 \text{ to } 2 = 2 \text{ to } 6;\ 2 \text{ to } 6 \div 2 = 1 \text{ to } 3.$$

A glorious proof of Mendelism! Those figures were not his own, but were an illustration drawn from Mr. Mudge's recent experiments on rats. A good deal had been heard about eye-colour, and the dominance of one kind of eye-colour. This was not a question of biometric method, but of the relative value of two sets of observations. He frankly confessed he did not trust Captain Hurst's judgment. A priori, he did not see why Captain Hurst's judgment as to what was a blue eye should be any better than Mr. Galton's. Everything depended on the way the eyes were put into categories. It was a case with the Mendelian of "Blue eyes, go to the right; brown eyes, go to the left." There was no gradation of any class at all. Whether Captain Hurst's results would be finally confirmed or not, he did not know. But when sections of the eye judged pigmentless in life were taken, pigment would be found microscopically, either in the iris or the choroid. He conjectured that by no other method could the presence or total absence of pigment in the eye be settled; neither the inspection with or without the ophthalmoscope could settle the total absence of pigmentation. This has been made

quite clear from the work on the eyes of albinos. The reason he referred to the difficulty last time of classifying albinos was that all grades of albinism were found in man; some were more frequent than others. And coming near to the limits of what was called "complete albinism," it was impossible to say whether any particular individual had some small amount of pigment or not. Probably only microscopic inspection after death could prove whether a person was partially pigmented or not. On examining the skin of an albino who had been clothed all his life, and the skin of an albino who had been working naked in the fields all his life, there would be found to be different degrees of pigment in the two. Again, the amount of pigment in the hair would vary according to whether the hair was observed in the summer or in the winter. These facts showed that one could not dogmatically state that all men were or were not albinos. The test that there was a complete absence of pigment was impossible of practical application. Partial albinism could not be differentiated, as Mr. Mudge asserted, as something pathological and distinct from complete albinism. It was inherited and occurred in albinotic stocks. The question of mice, for example, had been put forward. Mendelians constantly said there were two classes, mice with pink eyes and mice with black. Large breeding experiments had been undertaken to test such assertions, and the eyes of mice could not be simply classified into pink eyes and black eyes, into presence of pigment and the total absence of pigment. Intermediate eyes occurred, and again only by the microscopical examination of sections could the presence or total absence of pigment be known. Even if such investigation could be made, he asked how the medical man would be helped by the Mendelian. The answer was given in a recent paper by Mr. Punnett on "Applied Heredity"; Mr. Punnett said that the knowledge produced enabled one to predict the outcome of this or that given mating, and "would give to man such power of control over the living world as only a romancer would venture to dream of." That sentiment agreed with those Mr. Mudge had expressed that night. Now among the cases set up by Mr. Punnett as demonstrating Mendelism was the pedigree of the Doctors Weil, which had been cited by Professor Bateson. One of the Mendelian facts was that polyuria could not be inherited through a normal, and therefore medical men would no doubt tell the normal brothers and sisters of polyuric sufferers that if they married non-polyuric people they would produce non-polyuric offspring. But the completed Weil pedigree, as well as Dr. Gee's, give definite instances that polyuria can be inherited through normal individuals. What became of Mendelian prediction in

these cases? In nearly all series of pedigrees *one* could be chosen out which would "prove" Mendelism, but the next would "disprove" it, and it was only by the massing up of pedigrees, by examining very large numbers, that one could tell to what extent exceptions occurred to Mendelian rules.

He did not know anything of the inheritance of the dark skin of American Indians, but he had enquiries going on with regard to Eurasians, and he had made a very large number of enquiries of medical men living in the tropics as to crosses of negroes and whites. The cross produced was what was generally known as a mulatto. Then if two mulattoes bred together one ought to get 25 per cent. of white skins, 25 per cent. black skins, and 50 per cent. of something corresponding with the mulatto. When mulatto was crossed with white there ought to be 50 per cent. of white skins coming out, and when mulatto crossed with negro, 50 per cent. of negro skins. Did they get those returns to white skins and black skins? He would throw upon the screen slides which showed the answer to these questions. (Epidiascope and explanation.)

His correspondents all agreed that such segregation did not take place.

Such results did not lead him to assert that Mendelism did not hold for some human characters, but they caused him to pause and to ask his hearers to suspend their judgment until more material had been collected. It was not sufficient to take one or two pedigrees of special diseases and then say that Mendelism was a general rule for man. Ten or twelve years of collecting evidence was required, and at the end of that time they would know to what extent Mendelism did or did not apply. They knew from Mr. Nettleship and from others that night-blindness was inherited through non-normals as well as through normals. In other words, every stock did not show dominance of the same character. Yet Nettleship's night-blind pedigree, with its odds of millions to one against being a sample of a Mendelian population, had frequently been cited as an illustration of Mendelian principles. What he had to do on that occasion was not to stand up for his own statistical methods against an adversary who did not understand them. He could fight the whole question of chestnut horses, for example, from the purely observational standpoint. Captain Hurst wrote a paper, published by the Royal Society, and said that a chestnut horse was a horse that had *no black* in it, but one of the hard questions in practice was to distinguish a *black* chestnut from a black horse; and every intensity of chestnut, from the lightest red to black, could be found, and the exceptions, which Mr. Mudge

called errors of record, to the rule of chestnuts breeding chestnuts were a function of where the parents were taken in the scale of chestnut! With the existence of a *single* exception fell to the ground all the talk about dominants and recessives and "pure" gametes. Mendelism became only a statistical way of looking at things, and not a physiological law of inheritance. Mendelism could only be proved by Mendelians becoming vital statisticians—that is, adopting *biometric* methods. He had not replied to all Mr. Mudge's points, owing to the limitation of time, but he had suggested that there was a good deal more to be said on these points, and that from more than one side. Mr. Mudge's assertions needed wide qualification before acceptance.

Dr. Bulloch (London Hospital) said that after the discourses by Mr. Mudge and Professor Pearson he felt that anything he might contribute would be almost out of place. He desired to emphasize all he could what Professor Pearson said about pedigrees of human beings. He knew very little about Mendelism, and even less about Pearsonism, but he had been collecting for a number of years pedigrees which had been published concerning diseases in human beings, and he believed he was correct in saying that he had as complete a collection as had ever been brought together, and he had handed them to Professor Pearson to use in connexion with his new "Treasury of Human Inheritance." This important work should, he thought, receive the support of every member of the medical profession. Very few pedigrees which had been published in the last 200 years were of any use; certainly there were not twenty from all the hospitals. In the first number of Professor Pearson's "Treasury" he was publishing a complete collection of all the cases of polyuria. Only one was a good pedigree—namely, that of Weil. He (Dr. Bulloch) had a collection of fifty-one pedigrees of hermaphroditism and hypospadias, but not one of them was of value in settling the question. A case was recently published in the *Quarterly Journal of Medicine*. He pointed out to the contributor that there were certain deficiencies in the pedigree which, the cases being alive, he thought ought to be investigated. The net result of several letters was that that pedigree was now the best of any on the subject which had been published, and it would appear in Professor Pearson's "Treasury." His point was that data should be recorded far more carefully, and if some trouble were taken that could be done. When a number of really good pedigrees had been obtained it would be time enough to speak about theories of inheritance. He emphasized the need of pedigrees

being complete. In the East End of London pedigrees were difficult to obtain, but often a few postage stamps would assist greatly.

Mr. N. Bishop Harman, F.R.C.S., referring to the benefits to be derived from the study of anatomical peculiarities, *e.g.*, piebalds, said: One thing would appear to arise out of the learned papers that have been read before the Society during this important discussion on "Heredity," and that is that the medical profession is profoundly interested in the question of the applicability to man of the laws of heredity as propounded by Mendel. The question of the influence of heredity in the propagation of the diseases of the nervous system, of tuberculosis, and of cancer, has been debated at length, and in some instances widely diverse views have been taken; but from the trend of the several speeches made at the debate it would appear that we are attempting to obtain opinions on two very different points: (1) whether Mendel's law applies to man; (2) whether certain diseases are transmissible? Even supposing the latter be proved to be positive for some of the greater diatheses, as it has been already for some of the rarer diseases, particularly of the eye, it does not appear that from these conditions of disease we shall be able to gather satisfactory data for determining the first point—the applicability to man of Mendel's law of inheritance.

My communication to the debate will be in the nature of a suggestion and a concrete example of how that suggestion may be put to advantage. If we are to demonstrate the applicability or non-applicability to man of Mendel's law of inheritance it would seem that this can only be done by working out the pedigrees of families which present some well-marked and easily determined physical character. Forms of cataract, of night-blindness, or of colour-blindness do not fulfil this demand, for each of these conditions presents a serious disability to the unit, so that the unit affected by the condition has every inducement to hide or deny the existence of the defect. This has been pointed out by Mr. Nettleship and others as a reason for the failure of some pedigrees to conform numerically with Mendel's law. There are, however, some abnormal physical characters found in man which are at once easy of recognition and determination, and do not carry with them any social or pecuniary disability to the unit affected. One of these is a condition known as "piebald." It is a condition of parti-colouring of skin and hair, common enough in animals, but just sufficiently rare in man to render the cases that exist noteworthy. Further, the comparative

rarity of the condition in man makes every mating of an affected unit with one of the general population outside his or her own family a fresh crossing between two dissimilars—a self-coloured unit with a piebald unit.

At a recent meeting of the Ophthalmological Society I showed the pedigree of an English family for six generations in all of which a characteristic piebald mark could be traced. Six of the affected members were shown to the Society, and a large number of photographs from several childships. I show you now on the screen a lantern transparency of the photograph of the first member of this family I came across, and also the pedigree of this family. For full details of this family reference should be made to the original paper in the *Transactions of the Ophthalmological Society*, but I may be permitted to give a short note of them here. The inherited physical character is a sort of partial albinism; certain parts of an otherwise normal body are devoid of pigment. For the most part the characteristic markings are these: A white forelock, a white patch of skin spreading from beneath this white hair down the centre of the forehead like a "flare," and in some cases patches of white skin about the trunk or legs. The white tissues are appreciably more delicate than the normal skin and hair. The colour of the ordinary hair of the family ranges from light brown to a deep brown, almost black. In no case have I seen any parti-coloured irides or any whitening of the eyelashes; in one case only there were white tufts in the eyebrows. There have been no other physical anomalies found. There is a distinct tendency to an early "senile" whitening of the hair of the head, particularly in those whose hair is darkest, but the white lock is always distinguishable by its superior delicacy. The members of the family are long-lived, robust and intelligent. Six generations have been traced. Of these four are now living, and have been seen by me. The generations comprise thirty-four childships and 138 individuals. The piebald marking continues in a direct line of descent in these generations in nine childships and twenty-four individuals. In no case has there been any in-breeding between even remote degrees. The most outstanding features of the pedigree are these:—

(1) The piebald is conveyed by direct descent. Mother or father hands it down to the child.

(2) Once the piebald has been lost there is no evidence of a revival of the marking, so that an unmarked parent has an unmarked child.

(3) The children are not marked in proportion to the extent of the marking of the parent. One man who is the most marked of any of his childship has children and grandchildren amongst whom the marking

has appeared in very slight degree; it would seem to be dying out. One of his brothers, who is but little marked, has two childships by two wives, unrelated to each other or to himself, and all the eight children of the two wives are marked, some of them very strongly.

(4) Sex inheritance. In the first three generations of the pedigree the piebalds are all females, and the inheritance is through them only. This rule is broken in the next three generations, where males and females are affected in equal numbers, and the inheritance is through the males only.

(5) On Mendel's law Bateson, in the discussion on Mr. Nettleship's paper, "A History of Congenital Stationary Night-blindness in Nine Consecutive Generations,"[1] gave two tests which might be applied to determine the Mendelian character of an inheritance. "A Mendelian dominant might be tested in two different ways: (1) By the simple evidence that it was transmitted only by the affected; (2) if the case were of the simplest Mendelian type kind, then the offspring of the affected with an unaffected person should be *affected* and *unaffected* in equal numbers." Test 1 is true of this pedigree; the inheritance is only by the affected. Test 2 is true in the second generation; nearly true in the third generation (7 unaffected + 5 affected + 2 stillborn); it is not true in the fourth generation, for all the children of the one affected parent are affected; in the fifth generation it is true of two childships by two affected parents, but not true of two childships from one affected parent, for all the children are affected, and not true of one childship which escapes altogether; in the sixth generation it is not true, for only one of four children in the childship is affected.

It is evident from this enumeration that in some of the childships the inheritance has been in complete correspondence with the law of inheritance as propounded by Mendel himself: that when two unlike stocks are crossed all the progeny will be like one of them—"the dominant." Thrice in this pedigree affected units have produced complete childships of affected progeny. In four childships the inheritance has been equally divided according to Mr. Bateson's requirement. Only two cases are quite at fault—one where a woman slightly affected had two children not affected, and the other of a man whose marking was not according to usual type, and who only had one child in four affected.

There are certain points which one would like to comment upon. If the law of inheritance, according to some expositors, be held to show

[1] *Trans. Ophthal. Soc. U. K.*, 1908-9; xxix.

that a peculiar characteristic can only come by inheritance from those who already possess that characteristic, then Adam must have been a piebald! Else, how could this peculiar marking found in this family have arisen? It is certainly transmitted, and if it was not at some time acquired, then the self-coloured majority of humanity are recessives. Again, it has been said that a physical feature "apparently never disappears," and "could only be got rid of by the death of those who carried it" (Mr. Punnett in discussion on Mr. Nettleship's paper). Now, in this pedigree five piebalds got rid of the mark in some of their progeny, and one got rid of it completely; and from those unmarked children seventeen childships quite free from piebald have proceeded. The physical character has been got rid of, and therefore it would appear that an affected stock need not necessarily carry on the inheritance.

I do not suggest that one pedigree, however striking it may be, can go far to prove the truth of one or other theory of inheritance, but I do suggest the desirability of working out the pedigrees of these easily followed cases of piebald markings. The physical characteristic is such that it does not require a skilled and technical examination to determine its presence or absence, as is necessary in the case of congenital cataracts; there can be no dispute as to whether a subject is piebald or not, as may arise in suspected albinism; and there is the great advantage that when death has removed a member of a family there may still be photographs to demonstrate the presence of the physical characteristic.

Dr. C. Hubert Bond: It is with some diffidence that I take part in this discussion, for though I can contribute some recent figures I have in reality no new facts to offer, and at the utmost can only venture to offer a few suggestions. However, as one whose work is solely amidst a class of case that has been cited as specially prone to exhibit the effects of a faulty heredity, I am loth to let pass the opportunity thus given me of expressing myself as wholly in accord with those who believe in the paramount importance of hereditary influence. But I am not so sure that the influence of heredity is to be observed especially more in one disease, or in the diseases of one particular system, than in another. True, it may be more easy to observe in some, and it is also obviously a fact that the presence or consequences of certain diseases and abnormalities make themselves so conspicuously felt that the presence of the same in another member of the family becomes a fact of prominence and record, resulting in that particular affection being labelled as being peculiarly the outcome of hereditary taint. It is,

perhaps, an impertinence on my part, whose time is entirely occupied in the treatment of patients suffering from mental disease, to attempt to wander, in respect to the question of heredity, into speculations as to its importance in directions other than merely the mental malady. The insane, however, are liable to the same bodily affections as the sane, and in a community such as I have, of over 2,000 patients, many opportunities are afforded of observing facts outside the more obvious horizon of the mental affection—I say "the more obvious" because I submit that none of them can with safety be excluded, and that in considering the influence of heredity in any case of mental disease the inquiry as to hereditary taint should not be limited to the nervous system. Thus, in interviewing the father of an insane patient who himself may have always been free from mental or nervous affection, is it not of importance, for example, to note, if present, the same developmental abnormalities in both; that the son's baldness or his hair prematurely turning grey are repetitions of the same events at the same period of life as in the father; that both, perhaps, are liable to chronic bronchitis; or, again, that both have shown early liability to vascular degeneration, as depicted, *e.g.*, in the premature arcus senilis or in the visible network of cutaneous capillaries about the face or body? These examples could be multiplied many times, and I believe that none of such observations can with safety be overlooked. "A man is as old as his arteries" is a familiar aphorism. I suggest that a study of the influence of heredity as a determining factor in the age at onset of vascular degeneration is a point of no small importance in considering problems of heredity in mental affections, and I recognize that the essential underlying factor in such a study is not improbably a question of hereditarily faulty metabolism.

An endeavour to gauge the potency of any individual etiological factor among the many that have been scheduled for tabulation in respect to the statistics of mental diseases brings the inquirer at once face to face with the question of heredity—the factor that most of us, I think, have come to regard as the predominant one. Statistically this has not been proved; the family histories of cases admitted into asylums are often altogether lacking, or if obtained they very seldom approach completeness, and the obtaining of similar controlling information, complete or incomplete, gathered among the sane population has only just commenced to be attempted. This has been forcibly emphasized by other speakers, and I need not labour the point further.

I should, however, like to draw attention to some figures in the

nineteenth annual report (pp. 183-4) of the Asylums Committee of the London County Council, published this month. In that report the newly revised tables of the Medico-Psychological Association have been printed in full, and for the first time (on the pages I have quoted) it is possible to examine the correlation of any two factors on an extended scale. A quite cursory examination of the figures rapidly yields some interesting apparent etiological data. I say "apparent" because the first item—namely, that of 2,502 cases (males 1,222, females 1,280) whose present mental attack was believed to be the first one, and from whom imbeciles and idiots had been excluded, in 19 per cent. and in exactly equal proportion as to sex, one or more relatives had been found to be insane—is probably not strictly a fact, but a considerable under-estimate of the truth. The more complete are the family histories the greater does such a percentage tend to become. Nevertheless, such a confession does not, I think, seriously detract from the reliability of the following further data: Thus, from the same table may be learnt that of the 2,500 cases 6 per cent. (males 5 per cent., females 7 per cent.) belonged to the period of adolescence, and it is, I suggest, very significant to be able to note that the proportion of insane heredity in them rose to 26 per cent. (males 26 per cent., females 25 per cent.) in contrast with 19 per cent. among the whole. The cases which developed during senescence amounted to 9 per cent. (males 8 per cent., females 10 per cent.), and in them an insane heredity was found in only 9 per cent. (males 10 per cent., females 8 per cent.); in the 9 per cent. climacteric cases among the women 16 per cent. yielded an insane heredity. Such figures go to emphasize very strongly the potency of the stress of adolescence when exerted in a subject possessing the taint of insane heredity. The same table shows that an insane heredity was not specially associated with any other factor than adolescence, except in respect to cases which appeared to be precipitated by some variety of sudden mental stress; there were 5 per cent. of such cases, and in them insane heredity again rose to 26 per cent. (males 28 per cent., females 24 per cent.), but, then, of these cases only 7 per cent. (males 6 per cent., females 7 per cent.) belonged to the adolescent period, so that the intimacy between heredity and insanity during the developmental period is not disturbed by these figures.

The recitation of figures is always tedious, and I have only culled the foregoing—not too many, I trust—to illustrate the treasure-house such a method of tabulation may prove to be. To render it such, undoubtedly every effort should be strained to acquire full and complete

family histories. Such can never be possible in respect of anything approaching all the cases admitted to asylums, and it would probably be infinitely more valuable to tabulate cases in which the family history was reasonably complete separately from the general mass. The nature of the difficulties involved in obtaining such histories has already been sketched by others, but I should like to be permitted to take this opportunity to make one or two suggestions. A constant stumbling-block is that an important relative becomes lost sight of, and with every desire on the part of the friends of the patient to help the medical man, and with every willingness on the latter's part to spare himself no pains, he is baffled owing to inability to trace one or more of the more important of his patient's ancestors. The returns as to births and deaths made to the Registrar-General contain, as is proved by his annual and other reports, a storehouse of information, but I venture to suggest that the addition of certain extra items of information to the forms for the registration of births and deaths would prove of the utmost value to the seeker after family histories. Thus, in registering a death it would be desirable to not merely state the age, but as nearly as possible the actual date of birth of the deceased, and in the case of a married woman or widow her maiden name. Such information would usually be not difficult to obtain at the time of death and would materially assist in tracing, if desired, the deceased in the registers of births; the latter might well contain a column for cross-reference in which the fact of decease and date of such might be entered. Similarly, in registering the birth of a child, in addition to the full names of the parents now required, the dates of their birth, if demanded, would provide the necessary link of reference from one generation to another. And yet again, of extreme value to our present purpose, but perhaps too Utopian, would be the provision of columns stating the number such a child was in the offspring born of these particular parents (step-children, of course, excluded) and the full Christian names and dates of birth of brothers and sisters, whether then alive or not. Such extra information would, at the time of registration, be easy to obtain, and I cannot but feel that the extra clerical work involved would be amply repaid by the filling of the hiatus that now exists between the information concerning one generation and that of the next.

The PRESIDENT, in closing the debate, said he thought it would be agreed that the discussion had been extremely interesting, and somewhat profitable. He confessed it had wandered away at times from the

subject-matter of the discussion—"The Influence of Heredity on Disease." Disease, as he mentioned in his opening remarks, was a more complex matter than form or colour, with which the discussion had been chiefly concerned on the concluding day. He congratulated the Society on that its first general discussion since the formation of the Royal Society of Medicine.

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